Comments on Technology Assessment Report

Denosumab for the treatment of bone metastases from solid tumours

Amgen Limited

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Confidential information that is academic-in-confidence is highlighted and underlined

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Executive Summary

Comparator selection and relevant patient populations in Breast Cancer

- In breast cancer, NICE CG81 recommends the use of bisphosphonates in all patients, which is reflected by high bisphosphonate treatment rates in clinical practice (87% of patients with bone metastases).

Comparator selection and relevant patient populations in Prostate Cancer

- 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.
- The prior SRE patient subgroup from Study 103 is representative of the patients recommended a bisphosphonate in accordance with NICE CGs (painful bone metastases with history of a prior SRE). For example, 82% of patients with history of a prior SRE had pain at baseline.
- Continuous ongoing treatment with a bisphosphonate, as used within the denosumab phase III studies, reflects UK clinical practice. A UK chart review indicates that 49% are currently or previously treated with a bisphosphonate. Of those currently treated with a bisphosphonate, the majority (81%) are planned to receive continuous ongoing treatment for greater than 12 months.
- Denosumab represents a significant advance in treatment for all prostate cancer patients including those currently eligible for bisphosphonate treatment (i.e. those with painful bone metastases with a prior SRE). In addition to clinical superiority over zoledronic acid in the prevention of SREs, denosumab provides improved efficacy in the management of pain. Denosumab, unlike zoledronic acid, can also be used regardless of renal function, providing a safe and effective treatment for patients with renal impairment.

Comparator selection and relevant patient populations in Other Solid Tumours (OST)

- In patients with OST, where there are no NICE clinical guidelines recommending the use of bisphosphonates, expert opinion suggests that bisphosphonate usage is the same as in patients with prostate cancer (i.e. in patients with painful bone metastases and history of a prior SRE). This is supported by a UK chart review which shows that bisphosphonates are used in over 37% of patients with OST. Of these currently treated patients, 72% are intended to receive continuous ongoing bisphosphonate therapy for greater than 12 months.
- In the denosumab phase III OST study (Study 244); the patient subgroup who has experienced a prior SRE is representative of those OST patients who receive bisphosphonates within the UK. For example, 86% of patients with history of a prior SRE had pain at baseline.

Population vs. subgroup treatment effects used in the economic model

- 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. As indicated by the TAR, the denosumab phase III studies were not powered to detect a significant difference in efficacy in a sub-group of patients with a prior history of SRE.

Zoledronic acid patent expiry

- 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.

Efficacy of denosumab in the management of pain

- Pain, as a clinically important outcome, was rigorously assessed within the phase III studies using a range of pre-specified, exploratory endpoints. Although the studies were not individually powered to evaluate relative effectiveness in reducing pain; the results for each of the phase III studies and for the integrated analysis for the main pain endpoints showed a consistent benefit for denosumab over zoledronic acid in reducing pain.

Potential for perverse inequity in the bisphosphonate-contraindicated population

- 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.

Comparative efficacy used in the economic model

- The denosumab phase III studies represent the largest and most robust evidence package constructed to-date in SRE prevention in patients with bone metastases. 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. Comparative effectiveness synthesised through NMA methods can be of value in the absence of head-to-head RCTs, although as indicated in the TAR, NMA methods are subject to considerable uncertainty and need to be interpreted with caution.

1 Key assumptions and supporting information

In summary, we are in broad agreement with key findings in the TAR; namely that:

- Denosumab compared to zoledronic acid is effective in delaying time to first on study SRE and reducing the risk of multiple SREs for breast, prostate and OST; reporting that the results are mostly statistically significant and met the minimally clinically significant change described by clinical experts (i.e. a delay of more than 3 months and HR reduction of more than 20%).
- The impact of bone metastases on patients and the healthcare system is considerable. Bone metastases are associated with a worse prognosis, reduced quality of life and increased risk of complications and undoubtedly bone metastases and SREs require considerable healthcare resources.
- Denosumab's subcutaneous administration is advantageous compared with intravenous bisphosphonates both from a patient and NHS perspective. Subcutaneous administration requires a shorter time to administer, is associated with few complications, is technically easier and does not require hospital attendance.
- Denosumab dominates zoledronic acid in both breast cancer and prostate cancer regardless of prior SRE history (when including the PAS) and regardless of whether using clinical efficacy specific to prior SRE history subgroup or overall (pooled) efficacy across prior SRE subgroups within each tumor type. Denosumab is cost-effective (<£20-30K/QALY) compared with zoledronic acid in OST patients (including lung cancer) when appropriately using the overall (pooled) clinical efficacy of denosumab in the OST population.

We wish to provide supporting information related to the questions posed by the Academic Group in the TAR. These relate to the following elements discussed on page xxvii of the TAR:

- To what extent does the available data on SRE naive and SRE experienced patients reflect the likely patient groups for whom zoledronic acid is used? (See sections 1.1, 1.2 and 1.3)
- Is the manufacturer case review sufficient to conclude that most SRE experienced patients within the cancers reviewed are typically receiving bisphosphonates, leading to zoledronic acid being the appropriate comparator? (See sections 1.1, 1.2 and 1.3)
- Should the base case apply the SRE subgroup specific clinical effectiveness estimates? (See section 1.4)
- To what extent should zoledronic acid coming off patent in 2013 be considered? (See section 1.5)

We have also provided additional supporting information with regard to the following areas:

- Efficacy of denosumab in reducing pain (See section 1.6)
- Bisphosphonate contraindicated or intolerant population (See section 1.7)

- Comparative efficacy for economic modelling (See section 1.8)

1.1 Breast cancer comparator selection and relevant patient populations

1.1.1 In breast cancer, NICE CG81 recommends the use of bisphosphonates in all patients, which is reflected by high bisphosphonate treatment rates in clinical practice (87% of patients with bone metastases).

The TAR states *"For breast cancer, bisphosphonates are recommended for all patients with advanced breast cancer and newly diagnosed bone metastases (NICE clinical guideline (CG) 81)".* [Page xvii].
As indicated by the TAR, NICE clinical guidelines for breast cancer (CG81) recommend that bisphosphonates should be considered for use in advanced breast cancer patients with bone metastases. The adoption of these guidelines in clinical practice is reflected by high bisphosphonate treatment rates in breast cancer.

The TAR states *"Bisphosphonates are used consistently in breast cancer" [Page 14*].

We wish to confirm that this is supported by results of a UK patient chart review (Manufacturer Submission, Section 2.4.4) reporting that the majority of breast cancer patients (87%) received bisphosphonates.

The TAR states that "*Based on expert opinion zoledronic acid is the most widely used bisphosphonate* [*Page13].*

Zoledronic acid is the primary comparator in breast cancer since it is the most effective and represents the bisphosphonate most commonly used. We wish to confirm that this is supported by UK market share data (Manufacturer Submission, Section 2.4.4). This indicated that 50% of breast cancer patients treated with a bisphosphonate received zoledronic acid.

1.2 Prostate cancer comparator selection and relevant patient populations

1.2.1 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.

The TAR states, *"For prostate cancer, they (bisphosphonates) are recommended for men with hormone-refractory prostate cancer with painful bone metastases for whom other treatments (including analgesics and palliative radiotherapy) have failed (CG58)"* [Page xvi].

The current and relevant NICE clinical guidelines (CG58 and CG75) indicate that bisphosphonates are recommended in prostate cancer for patients with painful bone metastases who have a history of a prior SRE.

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.

In addition, the NICE clinical guideline (CG75) on the diagnosis and management of metastatic spinal cord compression (a defined SRE) recommends the use of bisphosphonates in patients with prostate cancer who have experienced spinal cord compression (SCC), if conventional analgesia fails. This therefore reinforces the CG58 recommendation that bisphosphonates be used in patients with prostate cancer to those with painful bone metastases who have experienced a prior SRE.

Therefore the relevant primary comparator for patients with prostate cancer is different for the two defined patient populations on the basis of the presence of painful bone metastases and SRE history (see Table 1).

Table 1. Relevant comparators based on NICE clinical guidelines CG58 and CG75

	Prostate cancer	
Population	No pain or pain with no prior SRE	Pain and prior SRE
Relevant comparator	Best supportive care	Bisphosphonates

1.2.2 The prior SRE patient subgroup from Study 103 is representative of the patients recommended a bisphosphonate in accordance with NICE CGs.

The TAR states, *"In the prostate cancer denosumab RCT (and the other two denosumab RCTs), in subgroup analysis, rather than presenting data on patients with painful bone metastases for whom other treatments have failed, the manufacturer presents data on patients with (i) no prior SRE and (ii) prior SRE. The results would be more generalisable if effectiveness data were presented for patients who had painful bone metastases despite conventional analgesic"* [Page 227].

The subgroup of patients from Study 103 with history of a prior SRE is representative of the bisphosphonate recommended patient population defined within NICE CG58 and CG75 i.e. prostate cancer patients with painful bone metastases who have failed analgesics and have had a prior SRE (i.e. radiation to the bone or SCC). Baseline characteristics and disease history for the prior SRE subgroup show that 78% of patients had received radiation therapy to the bone or spinal cord compression (SCC) whilst 82% had pain at baseline. In those patients with both a prior SRE and pain at baseline, 79% had radiation to the bone or SCC. Finally, in those patients with prior SRE of radiation to the bone or SCC and pain at baseline, 69% had used analgesics at baseline.

1.2.3 Continuous ongoing treatment with a bisphosphonate, as used within the denosumab phase III studies reflects UK clinical practice. A UK chart review indicates that the majority of patients with bone metastases receive continuous ongoing treatment for greater than 12 months with bisphosphonates.

The TAR states, "*There are some concerns around the reasonableness of the manufacturer argument that case review indicates the majority of patients have had or are likely to have treatment with bisphosphonates. These may be short courses rather than continuous ongoing treatment, the latter seeming to be the manufacturer intention in terms of denosumab use"* [Page 174] and additionally that "*It is not clear from the submission to what extent this bisphosphonate use is a short course, and to what extent it is ongoing continuous use of bisphosphonates"* [Page 142].

We wish to highlight that the patient chart review (Kantar Health 2010[1]) indicated the planned treatment duration with a bisphosphonate for those patients currently treated. Physicians planned to treat 65% patients with a bisphosphonate for an indefinite duration in prostate cancer. Additionally, physicians indicated 81% of patients were planned for treatment for a duration of greater than 12 months to indefinitely in prostate cancer (Table 2).

Table 2. Planned treatment duration with bisphosphonates by solid tumour type based on patient chart review

	Breast cancer	Prostate cancer	Other solid tumours
Sample size of patients currently treated (n)	323	245	115
Planned treatment duration			
<12 months	3%	14%	21%
12-23 months	4%	8%	4%
≥24 months	7%	8%	1%
Indefinitely	82%	65%	67%
Unknown	4%	5%	7%

1.2.4 Denosumab represents a significant advance in treatment for all prostate cancer patients including those currently eligible for bisphosphonate treatment (i.e. those with painful bone metastases with history of a prior SRE). In addition to clinical superiority over zoledronic acid in the prevention of SREs, denosumab provides improved efficacy for the management of pain. Denosumab, unlike zoledronic acid, can also be used regardless of renal function, providing a safe and effective treatment for patients with renal impairment.

The TAR states, *"Denosumab is licensed for the prevention of skeletal related events and not the treatment of bone pain"* [Page 218].

Denosumab, like zoledronic acid, is licensed for prevention of SREs (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumours. Also like zoledronic acid, denosumab is not specifically

indicated for the treatment of pain; however, it is indicated for the prevention of SREs including radiation to the bone, which is an intervention for the management of pain. However denosumab, unlike zoledronic acid, can be used regardless of renal function, providing a safe and effective treatment for patients with renal impairment. Additionally denosumab has demonstrated improved efficacy over zoledronic acid in the management of pain (Manufacturer Submission, Section 5.3.6.1 and Appendix IV). Further, because denosumab has proven superior efficacy over zoledronic acid in SRE prevention, this has been modelled to deliver superior overall health outcomes (in terms of QALYs gained) compared to zoledronic acid, at a lower cost. Therefore, regardless of the rationale for bisphosphonate use as recommended in NICE CGs, denosumab is a cost-effective alternative to zoledronic acid.

1.3 Other solid tumour comparator selection and relevant patient populations

1.3.1 In patients with OST, where there are no NICE clinical guidelines recommending the use of bisphosphonates, expert opinion suggests that bisphosphonate usage is the same as in patients with prostate cancer (i.e. in patients with painful bone metastases and history of a prior SRE). This is supported by a UK chart review which shows that bisphosphonates are used in over 37% of patients with OST.

Based on expert clinical opinion, it is understood that bisphosphonates are used selectively for the treatment of patients with OST in the same way that they are used in prostate cancer (patients with painful bone metastases and history of a prior SRE). A UK Chart Review (Manufacturer Submission, Section 2.4.4) shows that bisphosphonates are used in over one-third (37%) of patients with OST with bone metastases in the UK. Bisphosphonate use in patients with OST is lower than in prostate patients and this may reflect the poorer prognosis of OST patients. Furthermore, of patients treated with a bisphosphonate, physicians indicated that 72% would receive continuous ongoing therapy of either a duration greater than 12 months or indefinitely (Table 2).

Additionally, the TAR states, '*Expert opinion suggested that bisphosphonates, mainly zoledronic acid, were used in OST'* [page 25]

The findings of the Assessment Group, via independent expert opinion, suggest that zoledronic acid is the main bisphosphonate used in patients with OST. We wish to confirm that this is supported by results of UK market share data (Manufacturer Submission, Section 2.4.4). This indicated that 80% of OST patients treated with a bisphosphonate are given zoledronic acid.

1.3.2 In the denosumab phase III OST study (Study 244); the patient subgroup who has experienced a prior SRE is representative of those OST patients who receive bisphosphonates within the UK.

The subgroup of patients from Study 244 with history of a prior SRE is representative of the patient population treated with bisphosphonates in UK clinical practice; Baseline

characteristics and disease history for the prior SRE subgroup show that 76% of patients had received radiation therapy to the bone or spinal cord compression (SCC), whilst 86% had pain at baseline. In those patients with both a prior SRE and pain at baseline, 75% had radiation to the bone or SCC. Finally, in those patients with prior SRE of radiation to the bone or SCC and pain at baseline, 73% had used analgesics at baseline.

1.4 Population vs. subgroup treatment effects based on SRE history

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 the underpowered subgroup analyses: As indicated by the TAR, the denosumab phase III studies were not powered to detect a significant difference in efficacy in a sub-group of patients with a prior history of SRE.

The TAR states, *"The base case cost effectiveness results apply the clinical effectiveness estimates pooled across all patients for denosumab versus zoledronic acid. SRE naïve and SRE experienced clinical effectiveness estimates are available. Applying these considerably worsens the estimated number of SREs avoided and the QALY gain for denosumab compared to zoledronic acid among SRE experienced patients for prostate cancer and other solid tumours. Should the base case apply the SRE subgroup specific clinical effectiveness estimates?"* [page xxix].

We wish to reiterate that the denosumab phase III studies were powered to detect whether denosumab was non-inferior or superior to zoledronic acid with respect to preventing or delaying the time to first on-study occurrence of an SRE; and whether denosumab was superior to zoledronic acid in delaying the time to first-and-subsequent on-study SRE. The studies were not powered to detect differences in efficacy between treatments in subgroups. As acknowledged by the Academic Group in the TAR, *"However for those patients with an SRE at baseline there was only a significant difference in these outcomes in breast cancer. It should be noted that the trials were not powered to detect differences in these subgroups"* [page 230]. We would like to provide an example of the application of overall (pooled) clinical effectiveness estimates being used by the Institute when modelling subgroups. In Technology Appraisal 204 (Denosumab for the prevention of osteoporotic fractures in postmenopausal women, October 2010)[2] the Institute provides recommendations on the basis of patient subgroup risk factors for osteoporotic fractures (based on combinations of bone mineral density, age and the number of other independent clinical risk factors for fracture). This appraisal used overall (pooled) clinical effectiveness estimates for denosumab across these patient subgroups rather than utilising underpowered subgroup level estimates.

We believe that using underpowered subgroup efficacy is an inappropriate use of the largest and most robust evidence package constructed to-date in SRE prevention in patients with bone metastases. We recommend that overall (pooled) clinical efficacy from each study should be used as the basis of the economic evaluation of denosumab by tumour type.

1.5 Zoledronic acid patent expiry

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 following patent expiry in mid-2013 does not adhere with the Institute's *Guide to the methods of technology appraisal*[3] *(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.

1.6 Efficacy of denosumab in reducing pain

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).

1.7 Bisphosphonate contraindicated or intolerant population

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 prevents the potential for perverse inequity in access to an effective treatment in a patient group with a higher unmet need.

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 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.

1.8 Comparative efficacy for economic modelling

The denosumab phase III studies represent the largest and most robust evidence package constructed to-date in SRE prevention in patients with bone metastases. 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. Comparative effectiveness synthesised through NMA methods can be of value in the absence of head-to-head RCTs, although as indicated by the Assessment group, NMA methods are subject to considerable uncertainty and need to be interpreted with caution.

The TAR states, *"In terms of strengths, our review focused on RCTs, resulting in a high level of evidence. We undertook a NMA in order to provide an indirect estimate of the effectiveness of denosumab against relevant comparators that were not considered in the direct evidence. NMAs are not randomised comparisons but rather observational findings across studies and therefore the results of the NMA are subject to considerable uncertainty and should be interpreted with caution"* [page xxvi].

We acknowledge the necessity for comparative efficacy evidence synthesised through indirect or mixed treatment comparisons (network meta-analysis, NMA) for this appraisal given the additional potentially relevant comparators (i.e. other bisphosphonates and best supportive care) where no head-to-head RCT evidence exists.

Both the Academic Group (TAR Section 2, page xxvi) and Amgen (Manufacturer Submission, Section 5.4) have highlighted concerns regarding the considerable uncertainty and careful interpretation required for any evidence synthesised using NMA methods. We recommend that in the presence of head-to-head RCTs for denosumab compared to zoledronic acid, direct efficacy data from 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,*[3] *sections 5.3.13-22*).

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 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[4]*)* 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.

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).

Table 3. Summary of head-to-head evidence and comparative efficacy synthesised through NMA methods for time to first on-study SRE

	Time to first on-study SRE		
	Denosumab Phase III RCTs HR (95% CI)	**Manufacturer Submission NMA HR (95% CI)**	**Academic Group NMA HR (95% CI)**
Breast cancer			
Dmab vs. ZOL	0.82 (0.71, 0.95)	[redacted]	0.81 (0.78, 0.83)
Dmab vs. PAM	N/A	[redacted]	0.89 (0.86, 0.93)
Dmab vs. PBO	N/A	[redacted]	0.48 (0.46, 0.51)
Prostate cancer			
Dmab vs. ZOL	0.82 (0.71, 0.95)	[redacted]	**0.57 (0.54, 0.59)***
Dmab vs. PBO	N/A	[redacted]	0.45 (0.43, 0.48)
Other solid tumours (including NSCLC)			
Dmab vs. ZOL	0.81 (0.68, 0.96)	[redacted]	**0.93 (0.90, 0.96)***
Dmab vs. PBO	N/A	[redacted]	0.44 (0.42, 0.46)
Other solid tumours (excluding NSCLC)			
Dmab vs. ZOL	0.79 (0.62, 0.99)	Not performed	**0.93 (0.89, 0.96)***
Dmab vs. PBO	N/A	Not performed	0.37 (0.35, 0.39)
Non-small cell lung cancer			
Dmab vs. ZOL	0.84 (0.64, 1.10)	Not performed	0.79 (0.76, 0.81)
Dmab vs. PBO	N/A	Not performed	0.66 (0.63, 0.68)

*Note: Estimates in bold highlight where there are large inconsistencies between the phase III head-to-head RCT results and the Academic Group NMA. Abbreviations: RCT, randomised controlled trial; NMA, network meta-analysis; HR, hazard ratio; CI, confidence interval; Dmab, denosumab; PAM, disodium pamidronate; PBO, placebo; ZOL, zoledronic acid

Table 4. Summary of head-to-head evidence for and comparative efficacy synthesised through NMA methods for time to first-and-subsequent on-study SRE

	Time to first-and-subsequent on-study SRE		
	Denosumab Phase III RCTs RR (95% CI)	**Manufacturer Submission NMA RR (95% CI)**	**Academic Group NMA RR (95% CI)**
Breast cancer			
Dmab vs. ZOL	0.77 (0.66, 0.89)	[redacted]	0.75 (0.73, 0.76)
Dmab vs. PAM	N/A	[redacted]	0.57 (0.55, 0.59)
Dmab vs. PBO	N/A	[redacted]	0.42 (0.41, 0.43)
Prostate cancer			
Dmab vs. ZOL	0.82 (0.71, 0.94)	[redacted]	0.83 (0.81, 0.85)
Dmab vs. PBO	N/A	[redacted]	0.56 (0.54, 0.58)
Other solid tumours (including NSCLC)			
Dmab vs. ZOL	0.85 (0.72, 1.00)	[redacted]	0.87 (0.85, 0.89)
Dmab vs. PBO	N/A	[redacted]	0.63 (0.61, 0.66)
Other solid tumours (excluding NSCLC)			
Dmab vs. ZOL	0.83 (0.67, 1.03)	Not performed	0.82 (0.79, 0.84)
Dmab vs. PBO	N/A	Not performed	0.67 (0.64, 0.70)
Non-small cell lung cancer			
Dmab vs. ZOL	0.87 (0.68, 1.12)	Not performed	**0.97 (0.85, 1.01)***
Dmab vs. PBO	N/A	Not performed	0.69 (0.66, 0.73)

*Note: Estimates in bold highlight where there are large inconsistencies between the phase III head-to-head RCT results and the Academic Group NMA. Abbreviations: RCT, randomised controlled trial; AG, academic group; MS, manufacturer submission; NMA, network meta-analysis; RR, rate ratio; CI, confidence interval; Dmab, denosumab; PAM, disodium pamidronate; PBO, placebo; ZOL, zoledronic acid

2 Detailed Technical Clarifications

We wish to provide additional technical clarifications and information to support the finalisation of the TAR for the Appraisal Committee. The TAR contains some areas of technical or methodological uncertainty related to the clinical- and cost-effectiveness assessments which have been clarified in this section.

2.1 Clinical effectiveness

2.1.1 Clinical methodology of the denosumab Phase IIII Studies

2.1.1.1 Selection of SRE within the 21-day window

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 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.

2.1.1.2 Composite endpoint

The TAR states, *"Uncertainties - SREs are composite endpoints. Therefore higher event rates and larger treatment effects that are associated with the less important components of a composite endpoint could result in a misleading impression of the treatment's effectiveness in relation to components that are clinically more important but occur less frequently"* [page 228].

The composite SRE endpoint used within each of the denosumab phase III studies was defined as pathologic fractures, spinal cord compression, radiation to bone, and surgery to bone. The selection of this composite end point was based on precedent with other approved products and advice received from regulatory authorities. As a result, the definition and assessment of SREs for the primary efficacy analyses in the denosumab studies are consistent with those used in the registrational studies supporting the approval of the active comparator, zoledronic acid, for this indication.

All of the component SRE events are clinically meaningful and indicative of uncontrolled metastatic disease within the bone which becomes symptomatic or requires more aggressive management. This composite endpoint is considered to capture data on all clinically relevant events and is more likely to detect therapeutic benefits when treatment effects and disease morbidity is multifaceted.

In addition the assumptions used in the economic model were very conservative in favour of less effective interventions, with the costs of vertebral fractures being excluded.

2.1.1.3 Patients with renal impairment:

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[5] 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 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[5]

2.1.2 Efficacy in Patients with Non-Small Cell Lung Cancer (NSCLC)

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.

2.1.3 Patients with osteolytic and osteoblastic lesions:

The TAR states, *"Prostate cancer generally results in predominantly osteoblastic lesions and breast cancer predominantly osteolytic lesions. Theoretically there may be a difference in the efficacy of denosumab depending on the predominant type of bone lesion' The pivotal denosumab studies did not report a subgroup of patients by lesion type*" [page 231].

We wish to highlight that denosumab has demonstrated superior efficacy over zoledronic acid in both breast (predominantly osteolytic) and prostate cancer (predominantly osteoblastic).

2.1.4 Breast cancer network meta-analysis

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[6] was used as a supplementary data source for the Novartis 010 Study (Rosen 2003)[7] 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 (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)[7] using methods proposed by Tierney 2007[8]. We recommend that the HR reported in the FDA Statistical Review and Evaluation of Zometa[6] are utilised instead for zoledronic acid versus disodium pamidronate in accordance with recommendations cited by Tierney[8] (*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.

2.2 Cost-effectiveness

2.2.1 Drug acquisition, administration and staff costs

2.2.1.1 Drug acquisition costs

The TAR states, *"The manufacturer cites the BNF as the source of the direct drug costs of the comparators. The BNF used by the manufacturer may predate the current BNF62"* [TAR page 151, paragraph 6].

We wish to confirm that BNF61 (March 2011) was used for drug costs in the evidence submission. This was subsequently superseded by BNF62 (September 2011) following our evidence submission in July 2011.

2.2.1.2 Drug administration and staffing costs (micro-costing study)

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.

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 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.

Finally, the TAR states that *"It is unclear to what extent any of the nursing staff would have had actual experience of denosumab, but they would obviously be fully familiar with subcutaneous injection."* We wish to confirm that the oncology nurses were not required to have direct experience with denosumab to participate. They were required to have experience in the administration of at least one of the intravenous bisphosphonates. All the healthcare professionals were provided with a profile of denosumab with respect to the pharmaceutical formulation and posology of administration to allow appropriate quantification of the staffing, time and materials required to administer a single dose.

We recommend the factual inaccuracies in the TAR are amended to reflect the healthcare professionals surveyed and the questionnaire methodology regarding intravenous infusion times.

2.2.1.3 Doses withheld

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)[9]. 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) 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.

2.2.2 Skeletal-related events

2.2.2.1 The cost of skeletal-related events

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)[10] 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)[11]. 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 consequential removal of excess bed day costs resulting in an underestimation in the costs of SRE management to the NHS.

2.2.2.2 Radiotherapy

The TAR states, "*For reasons that are not clear, to cost radiotherapy planning and administration the manufacturer uses 2008-09 NHS reference costs and indexes these for inflation, rather than using the 2009-10 NHS reference costs which are employed for all the other SREs*" [page 156, paragraph 1].

We wish to confirm that there was an unintentional difference in costing sources for radiotherapy and other SREs (pathological fractures, spinal cord compression and surgery to bone) in our evidence submission. This discrepancy was introduced following an update to the economic unit costs following the publication of NHS Reference Costs 2009-10[11].

2.2.3 Quality of life

2.2.3.1 Quality of life based on the denosumab phase III studies

We wish to provide further clarification regarding the EQ-5D analysis and related section in the TAR [Section 11.2.5, Quality of life, pages 158-164] in addition to the information provided in the evidence submission.

TAR: *"For fractures, it is not obvious why the extended period of time prior to the fracture being identified is required" [page 158]*.

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.

TAR: *"The submission and its appendices provide no detail of the functional forms that were tested during the EQ-5D data analysis. No statistical justification for the functional form chosen by the manufacturer over other candidate functional forms is presented"* [page 158]

We wish to confirm that the choice of candidate functional forms was made *a priori.* The following distributions were considered in the model: normal distribution, gamma distribution. The normal distribution gives a good fit if the distribution of the utility decrements is not skewed and the gamma is likely to give a good fit if the utility decrements are right skewed.

TAR: *"Other covariates not included within the manufacturer model might be anticipated to be significant, and it might also be anticipated that there could be a general cancer specific time trend to the patient HRQoL, such as that within the van den Hout reference summarised in the quality of life review above. Not considering progression within the modelling of utility is surprising"* [page 158] and *"There is also no provision for other elements of the cancers, such as progression, to affect patient quality of life which may have led to bias"* [page 162].

We wish to highlight that the aim was to keep the model as parsimonious as possible since it involved simultaneously fitting many covariates of interest with a correlation structure over time. As a result, their needed to be sufficient data to reliably estimate any single visit's correlation to other visits and also all the covariates for each visit included in the model. Since smaller numbers of subjects have data for the later visits, additional covariates that are included may have resulted in some of the later visits no longer able to be included in order to allow the model to converge and reach stability.

With respect to progression, we do not believe that this would have affected the change in baseline utility between SRE naive and SRE experienced patients due to the following reasons. Firstly, progression was originally included and was estimated to have only a small impact. Secondly, the impact of progression was also approximated by including a time variable as a main effect; however the impact of this was very small and not significant. Since the impact of time in the model was found to be very small and in the interests of a model that does not have the impact of the SRE or AE conditional on the length of time in the study it was appropriate to omit it from the model.

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 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.

2.2.3.2 Discounting of QALYs

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.

2.2.3.3 Application of disutility prior to start of treatment

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 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.

2.2.3.4 Double counting of health benefits

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.

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.

3 Factual Inaccuracies

We wish to highlight the following factual inaccuracies within the TAR described in below (Table 5) and the recommended corrections.

Table 5. Factual inaccuracies in the TAR

Technology Assessment Report Section	Factual Inaccuracy	Recommended Correction
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.
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
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%)
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"
Page 43	Section on Prior history of SRE - refers to Study 103 which is incorrect	Should refer to Study 136
Page 48	Section on SRE by type: Last sentence "….for spinal cord compression (0.07 versus 1.75)" is incorrect.	The value 1.75 should be 0.37
Page 69, Table 21	Fizazi denosumab column Ethnicity other - 121 (135) is incorrect	Should be 121 (13%) not 121 (135)
Page 76	"….[redacted] SREs occurred in [redacted] patient-years in the denosumab arm and [redacted] occurred in [redacted] patient-years…."	Marked as academic in confidence in the manufacturer's submission
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)

Page 97	"The study by Henry and colleagues reported a statistically significant difference in favour of denosumab for overall survival (21% risk reduction with denosumab) but in OST not NSCLC as per Section 8",	Need to make clear what which cancer population this refers to.
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
Page 106	First paragraph: is not reported in Henry reference	Need to indicate where this information comes from
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
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
Page 116	'10% of denosumab treated patients' is incorrect	Should be 10.8% not 10% for the denosumab group
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
Page 120	Denosumab group 10% is incorrect	Should be 10.8% not 10% for the denosumab group
Page 145, Table 70	SRE naïve for OST is incorrect	SRE naïve for OST is 51% or 49% for OST excluding MM
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 experienced subgroup for this comparison.	Amgen modelled the SRE naive subgroup for comparisons with best supportive care
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.

4 References

[1] Amgen. Data on file: Kantar Health – Patient Chart Review. 2010.

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[4] Woods BS, Hawkins N, Scott DA. Network meta-analysis on the log-hazard scale, combining count and hazard ratio statistics accounting for multi-arm trials: A tutorial. BMC Med Res Methodol 2010;10.

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