# Systematic review of the clinical effectiveness and cost-effectiveness, and economic evaluation, of denosumab for the treatment of bone metastases from solid tumours

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**Rider on responsibility for report**

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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**Contributions of authors**

Pam Royle developed the protocol, ran the search strategies and obtained papers. Fiona Stewart obtained papers, managed the reference database and formatted references. John Ford and Pam Royle screened the search results, assessed full text studies for inclusion, and along with Pawana Sharma undertook data extraction and quality assessment. John Ford drafted the background chapter, Pawana Sharma drafted the methods chapter and Pawana Sharma, John Ford and Graham Mowatt drafted the clinical effectiveness results chapters. Ewen Cummins undertook the economic modelling and drafted the chapters on cost-effectiveness and the critique of the manufacturer's submission. Rhona Johnston helped to

build the economic model. Andrew Elders conducted the statistical analysis. Rob Jones, Clive Mulatero and Radha Todd provided expert advice on clinical aspects of the review. All authors assisted in preparing the manuscript and commenting on drafts.

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# 1 DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

| | | | |
|---|---|---|---|
| **AE** | Adverse event | **MRI** | Magnetic resonance imaging |
| **AG** | Assessment Group | **MS** | Manufacturer submission |
| **ASCO** | American Society of Clinical Oncology | **NICE** | National Institute for Health and Clinical excellence |
| **AUC** | Area under the curve | **NMA** | Network meta-analysis |
| **BP** | Bisphosphonate | **NSAID** | Non-steroidal anti-inflammatory drug |
| **BPI-SF** | Brief Pain Inventory – Short Form | **NSCLC** | Non-small cell lung cancer |
| **BSAP** | Bone specific alkaline phosphotase | **NTX** | Urinary collagen type 1 cross-linked N-telopeptide |
| **BSC** | Best supportive care | **ONJ** | Osteonecrosis of the jaw |
| **CEAF** | Cost-effectiveness acceptability frontier | **OR** | Odds ratio |
| **CG** | Clinical guideline | **PAS** | Patient Access Scheme |
| **CI** | Confidence interval | **PET** | Positron emission tomography |
| **CHMP** | Committee for Medicinal Products for Human Use | **PINP** | N-terminal type 1 procollagen peptide |
| **CRPC** | Castration-resistant prostate cancer | **PR** | Progesterone receptor |
| **CSPC** | Castration-sensitive prostate cancer | **PSA** | Prostate-specific antigen |
| **CSR** | Clinical study report | **PSSRU** | Personal Social Services Research Unit |
| **CT** | Computed tomography | **QALY** | Quality adjusted life year |
| **CTCAE** | Common Terminology Criteria for Adverse Events | **RANK L** | Receptor activator of nuclear factor kappa-B ligand |
| **CTX** | Urinary or serum collagen type 1 cross-linked C-telopeptide | **RCT** | Randomised controlled trial |
| **ECOG** | Eastern Oncology Cooperative Group | **RR** | Relative risk |
| **ER** | Oestrogen receptor | **SCC** | Spinal cord compression |
| **FACT** | Functional Assessment of Cancer Therapy | **SCLC** | Small cell lung cancer |
| **FACT-B** | Functional Assessment of Cancer Therapy – Breast | **SD** | Standard deviation |
| **FACT-G** | Functional Assessment of Cancer Therapy - General | **SIGN** | Scottish Intercollegiate Guidelines Network |
| **FACT-P** | Functional Assessment of Cancer Therapy - Prostate | **SMPR** | Skeletal morbidity period rate |
| **HCM** | Hypercalcaemia of malignancy | **SMR** | Skeletal morbidity rate |
| **HER 2** | Human epidermal growth factor receptor 2 | **SPECT** | Single-photon emission computed tomography |
| **HR** | Hazard ratio | **SRE** | Skeletal related event |

| | | | |
|---|---|---|---|
| **HRQOL** | Health related quality of life | **TNM** | Tumour node metastasis |
| **ISPOR** | International Society for Pharmacoeconomics and Outcomes | **TOI** | Trial outcome index |
| **LDH** | Lactate dehydrogenase | **VAS** | Visual analogue scale |
| **MCMC** | Markov chain Monte Carlo | **ZA** | Zoledronic acid |
| **MM** | Multiple myeloma | | |

## 2 EXECUTIVE SUMMARY

### Background

Bone is a common site of spread (metastasis) of cancer in many solid tumours, but especially ones that start in the breast, prostate or lung. Bone metastases are associated with a worse prognosis, reduced quality of life and increased risk of complications. The term 'skeletal related event' (SRE) is used to group the following complications together: pathological fracture, spinal cord compression, and radiotherapy or surgery to bone. Bisphosphonates can be used to prevent SREs or treat bone pain in cases where conventional analgesics have failed. Four bisphosphonates are licensed in the UK for treatment of bone metastases from solid tumours: zoledronic acid (intravenous administration), disodium pamidronate (intravenous), ibandronic acid (intravenous or oral) or sodium clodronate (oral). Only zoledronic acid is licensed in the management of bone metastases from all advanced solid tumours, the others are restricted to breast cancer. Patients who are not treated with bisphosphonates receive best supportive care (BSC), which can vary depending on the type of primary cancer but may include chemotherapy, palliative radiotherapy, antibiotics, steroids, analgesics or surgery. The specific place of bisphosphonates in the care pathway varies. For breast cancer, bisphosphonates are recommended for all patients with advanced breast cancer and newly diagnosed bone metastases (NICE clinical guideline (CG) 81). For prostate cancer, they are recommended for men with hormone-refractory prostate cancer with painful bone metastases for whom other treatments (including analgesics and palliative radiotherapy) have failed (CG 58). For lung cancer (CG 121) and other solid tumours there is no clear guidance on when bisphosphonates should be administered. Denosumab (Xgeva), administered by subcutaneous injection every four weeks, offers an alternative therapy to bisphosphonates and/or best supportive care for the prevention of SREs in patients with bone metastases from solid tumours.

### Objectives

The aim of this review was to assess the clinical and cost effectiveness of denosumab, within its licensed indication, for the treatment of bone metastases from breast, prostate, non-small cell lung (NSCLC) or other solid tumours.

### Methods

Electronic searches were undertaken to identify published and unpublished reports. The databases searched included MEDLINE, EMBASE, The Cochrane Library and Web of Science with Conference Proceedings. Other sources including the 2010 and 2011 meeting

abstracts of the American Society of Clinical Oncology, American Urological Association and San Antonio Breast Cancer symposium were also searched. The date of the last searches was July 2011. The types of studies considered were systematic reviews or randomised controlled trials (RCTs); observational studies were also considered for data on safety. Participants had breast, prostate, lung cancer or other solid tumours and at least one bone metastasis. The intervention considered was denosumab compared with either bisphosphonates or BSC. Outcome measures included time to first on-study SRE, risk of first-and-subsequent SREs, incidence of SREs, hypercalcaemia, overall survival, pain, health-related quality of life and adverse events related to treatment.

Two reviewers screened the titles and abstracts of all reports identified by the search strategy. Data extraction and quality assessment were undertaken by one reviewer and checked by a second reviewer. The quality of the RCTs was assessed using the Cochrane risk of bias tool. As scoping searches had indicated there were no direct comparisons of denosumab with bisphosphonates (other than zoledronic acid) or BSC we planned to undertake a network meta-analysis (NMA), pooling direct and indirect evidence in a single analysis in order to obtain an indirect estimate of the relative effectiveness of denosumab against these comparators. Time to first on-study SRE was reported as hazard ratio (HR) and 95% confidence interval (CI) while risk of first-and-subsequent SREs was reported as rate ratios (RR) and 95% CI.

The economic modelling approach adopted was to amend the inputs to the manufacturer model to revise the base case estimates, coupled with some additional sensitivity analyses around clinical inputs and costs. The impact of the results from the assessment group NMA were then applied and contrasted with those of the manufacturer. The assessment group then rebuilt the manufacturer model as a cross check and to enable the introduction of the structural model elements of (i) spinal cord compression having a sustained impact on quality of life beyond five months from diagnosis, and (ii) a decay in quality of life in the final year. This was coupled with additional sensitivity analyses.

**Results**

***Description of studies***

Thirty-nine studies met the inclusion criteria for the review of clinical effectiveness. Of these, 31 did not contribute data to the NMA and none reported denosumab. Eight studies were included in the NMA, of which four studies involving more than 3,700 patients reported breast cancer (denosumab versus zoledronic acid [Stopeck 2010]; zoledronic acid versus pamidronate [Rosen 2003a]; zoledronic acid versus placebo [Kohno 2005]; pamidronate

versus placebo [Lipton 2000]), two studies involving more than 2,300 patients reported prostate cancer (denosumab versus zoledronic acid [Fizazi 2011]; zoledronic acid versus placebo [Saad 2002]) and two studies involving more than 2,100 patients reported other solid tumours (denosumab versus zoledronic acid [Henry 2011]; zoledronic acid versus placebo [Rosen 2003b]), with both studies including subgroups of (i) NSCLC (n=946) and (ii) other solid tumours excluding NSCLC (n=1164). The largest studies were the three reporting denosumab: breast cancer (n=2046), prostate cancer (n=1901) and other solid tumours (n=1597).

***Quality of studies***

All studies were generally of good quality. Three of the breast cancer studies (Stopeck 2010, Lipton 2000, Rosen 2003a) were multicentre and international, while the fourth (Kohno 2005) was multicentre and set in Japan. In three of these studies sequence generation and allocation concealment were considered adequate, while in the fourth (Stopeck 2010) these aspects were considered unclear due to insufficient information. Both prostate cancer studies (Fizazi 2011, Saad 2002) were multicentre, international RCTS in which sequence generation and allocation concealment were considered adequate. Of the two studies reporting other solid tumours, in one (Henry 2011) sequence generation and allocation concealment were considered adequate while in the other (Rosen 2003b) this was unclear due to insufficient information.

***Summary of risk/benefits***

In terms of the direct evidence, for breast cancer, there was a statistically significant difference in favour of denosumab compared with zoledronic acid for the time to first on-study SRE for all patients (HR 0.82, 95% CI 0.71 to 0.95; not reached versus median 26.4 months)

For prostate cancer, there was a statistically significant difference in favour of denosumab compared with zoledronic acid for the time to first on-study SRE for all patients (HR 0.82, 95% CI 0.71 to 0.95; median 20.7 versus 17.1 months) and for those with no prior SRE (HR 0.80, 95% CI 0.67 to 0.95)

[redacted]

For the subgroup of patients with NSCLC, the time to first-on-study SRE for all patients favoured denosumab without being statistically significant (HR 0.84, 95% CI 0.64 to 1.10; [redacted]. For the subgroup of patients with other solid tumours excluding NSCLC, there was a statistically significant difference in favour of denosumab for median time to first on-study SRE for all patients (HR 0.79, 95% CI 0.62 to 0.99; [redacted]

For other solid tumours including NSCLC, there was a statistically significant difference in favour of denosumab for time to first on-study SRE for all patients [redacted]. For risk of developing first-and-subsequent SREs, for all patients, the difference was borderline significant in favour of denosumab [redacted].

In the denosumab studies the vast majority of SREs consisted of pathological fracture and radiation to bone while there were few occurrences of spinal cord compression or surgery to bone. Overall survival was similar between the treatment groups in the three studies apart from an ad hoc analysis of the subgroup with NSCLC which reported a statistically significant difference in favour of denosumab (HR 0.79, 95% CI 0.65 to 0.95). However this was a subgroup of a study that was not powered to detect differences in overall survival and until further evidence becomes available this result should be interpreted with caution.

Denosumab delayed the time to development of moderate or severe worst pain (worst pain score of > 4 points) compared with zoledronic acid (breast cancer: [redacted]; prostate cancer: HR 0.89, 95% CI 0.77 to 1.04; median 5.8 versus 4.9 months; other solid tumours including NSCLC: [redacted]. In all three studies, in terms of quality of life, overall mean FACT scores remained similar between the groups, [redacted].

In terms of adverse events, for breast cancer, prostate cancer and other solid tumours respectively, there were more occurrences of hypocalcaemia in the denosumab group compared with the zoledronic acid group (5.5% versus 3.4%; 12.8% versus 5.8%; 10.8% versus 5.8%), rates of ONJ were slightly higher (2.0% versus 1.4%; 2.3% versus 1.3%; 1.3% versus 1.1%), while there were lower rates of events associated with renal impairment (4.9% versus 8.5%; 14.7% versus 16.2%; 8.3% versus 10.9%) and acute phase reactions (10.4% versus 27.3%; 8.4% versus 17.8%; 6.9% versus 14.5%). For hypercalcaemia, [redacted].

In terms of the network meta-analyses, for breast cancer, prostate cancer and other solid tumours including NSCLC, the Assessment Group's NMA reported a statistically significant difference in favour of denosumab compared with placebo for both time to first on-study SRE (HR 0.48, 95% CI 0.46 to 0.51; HR 0.45, 95% CI 0.43 to 0.48; and HR 0.44, 95% CI 0.42 to 0.46 respectively) and risk of first-and subsequent SREs (RR 0.42, 95% CI 0.41 to 0.43; RR 0.56, 95% CI 0.54 to 0.58; RR 0.63, 95% CI 0.61 to 0.66 respectively), [redacted]. For NSCLC, and other solid tumours excluding NSCLC, the Assessment Group's NMA reported a statistically significant difference in favour of denosumab compared with placebo for both time to first on-study SRE (HR 0.66, 95% CI 0.63 to 0.68 and HR 0.37, 95% CI 0.35 to 0.39 respectively) and risk of first-and-subsequent SREs (RR 0.69, 95% CI 0.66 to 0.73 and RR 0.67, 95% CI 0.64 to 0.70 respectively). The manufacturer's NMA did not report these latter two outcomes.

***Summary of costs***

The manufacturer estimates through a survey of oncology doctors and nurses that denosumab will result in staff time savings compared to zoledronic acid of around [redacted] minutes per administration. These arise in part from the pre-administration savings of about [redacted] minutes, but more from drug administration savings of [redacted] minutes within which avoiding the need for infusion saves [redacted] minutes of staff time. This latter was not included within the initial survey, but was subsequently added by the manufacturer.

Taking these elements together with the consumables and fixed costs estimated within the micro-costing study yields the following total annual direct drug and administration costs as

per the manufacturer: denosumab £4,466.80 without PAS, [redacted]; zoledronic acid £3,364.66 (British National Formulary (BNF) 62 states £3,245.97); pamidronate £4,117.23 (BNF 62 states £4,081.74); ibandronic acid (intravenous) £3,369.73; and ibandronic acid (oral) £2,464.80. These costs do not include withheld doses due to poor renal function. Without the PAS the annual denosumab cost of £4,467 is around £1,102 more expensive than zoledronic acid.

The PAS proposed by the manufacturer has recently been approved. [redacted]

[redacted]

Among those receiving 3 weekly IV chemotherapy the likelihood is that any IV bisphosphonates would also be administered 3 weekly. Whether denosumab would be administered on a 3 weekly basis in this situation is a moot point. Four weekly dosing through either an additional outpatient visit or possibly a dedicated health visitor domestic visit would seem a possibility.

***Summary of cost-effectiveness***

The manufacturer case is broadly that while the average patient benefits from the reduced number of SREs is not large, [redacted]

[redacted]

[redacted]Manufacturer cost effectiveness estimates for denosumab compared to BSC are

typically in excess of £100k per QALY, and even with the PAS are closer to £100k per QALY than £50k per QALY.

Assessment group within trial analyses suggest that for breast cancer patients denosumab results in a slightly lower average number of SREs compared to zoledronic acid, and that this will translate into a small average annual gain of perhaps 0.003 to 0.006 QALYs: roughly equivalent to one to two additional days in full health or two to three days at the SRE naïve average quality of life. Without the PAS the additional cost of denosumab does not justify these relatively minor gains. With the PAS denosumab is estimated to be broadly cost neutral to slightly cost saving, and so cost effective compared to zoledronic acid. If the price of zoledronic acid falls only slightly at patent expiry, the cost effectiveness of denosumab compared to it will worsen dramatically due to the very small estimate of patient gains.

Within trial analyses suggest that for prostate cancer patients denosumab results in a slightly lower average number of SREs compared to zoledronic acid. This translates into a slightly larger additional average annual gain of perhaps 0.008 to 0.016 QALYs. The reason for this difference in prostate cancer is the greater proportion of spinal cord compressions within the overall number of SREs. 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. This aspect is not considered in either the manufacturer model or the AG economic model.

Without the PAS the additional cost of denosumab still does not justify the relatively minor estimated gains. With the PAS, [redacted] is estimated as to increase annual costs by around £100 which translates into cost effectiveness estimates of between £6,545 per QALY and £15,272 per QALY. But this AG within trial analysis does not distinguish between SRE naïve and SRE experienced patients.

Given the slightly larger patient gains estimated for prostate cancer patients from denosumab, its cost effectiveness compared with zoledronic acid is not as sensitive to the price of zoledronic acid as breast cancer. But the fall in the price of zoledronic acid need not be large to make denosumab not cost effective.

For the cost utility modelling within breast cancer, the lifetime gains across all patients are estimated to be around 0.013 QALYs. This is again small, and does not justify the additional cost of £1,691 per patient compared to zoledronic acid. With the PAS [redacted]

[redacted] denosumab is estimated to dominate zoledronic acid. But for those contraindicated to bisphosphonates the cost effectiveness is poor: even with the PAS the cost effectiveness is £158,844 per QALY. Applying the SRE naïve and SRE experienced subgroup specific clinical effectiveness has little impact upon the results, as these estimates are reasonably close to the pooled all patient estimates.

For the cost utility modelling within prostate cancer, across all patients the gain from denosumab over zoledronic acid is around 0.020 QALY while compared to BSC it is 0.030 QALYs, at net costs without the PAS of £941 and £3,880 respectively. Without the PAS, compared to zoledronic acid this results in a cost effectiveness of £46,976 per QALY. Cost effectiveness is estimated to be slightly better among the SRE naïve at £35,732 per QALY, but the quid pro quo is a worse cost effectiveness among the SRE experienced of £167,503 per QALY. This may arise in large part due to the estimated step change in HRQoL arising from a patient's first SRE.

With the PAS, denosumab is estimated to be cost saving compared to zoledronic acid and so dominate it. For those contraindicated to bisphosphonates, denosumab is not estimated to be cost effective compared to BSC.

Applying the SRE naïve and SRE experienced subgroup specific clinical effectiveness has a reasonably large impact upon the results. The impact of this on the modelling is not symmetric. As the model progresses, more patients fall into the SRE experienced group and as a consequence the estimated cost effectiveness of denosumab worsens. But the PAS is still sufficient for [redacted] denosumab being estimated to remain dominant over zoledronic acid.

Within the cost utility modelling of other solid tumours including lung, the gains from denosumab over zoledronic acid are estimated to be less than 0.01 QALYs. Without the PAS denosumab is not cost effective, but with it the small additional overall costs of around £100 result in cost effectiveness estimates of between £11,800 per QALY and £13,900 per QALY. The impact of applying the SRE subgroup specific estimates within this group is quite large. While it improves the estimates cost effectiveness of denosumab compared to BSC for SRE naïve patients, even with the PAS it is not sufficient to render it cost effective. Due to the SRE experienced relative risk for SREs being only [redacted] compared to zoledronic acid, the cost effectiveness estimate for denosumab worsens to £38,458 per QALY compared to zoledronic acid among these patients.

For lung cancer, possibly due to the short life expectancy, the patient gains from denosumab over zoledronic acid among SRE experienced patients are estimated to be small: 0.003 QALYs. Even with the PAS, the additional cost of £118 results in a cost effectiveness of £42,698 per QALY.

***Sensitivity analysis***

A concern within the modelling is BSC being assumed to have a zero incidence of the modelled SAEs. When the benefits from active treatments upon SREs are muted, there is the possibility that SAEs come to the fore and require a more detailed consideration. Sensitivity analyses that completely exclude SAEs from the analysis do improve the cost effectiveness of denosumab compared to BSC, but this in itself is not sufficient to render denosumab cost effective. Even with the PAS, all but one of the cost effectiveness estimates remain above £50k per QALY with a large majority being above £100k per QALY. The exception is the cost effectiveness estimate for SRE naïve prostate cancer patients, which within the pooled clinical effectiveness estimates analysis sees denosumab have a cost effectiveness estimate compared to BSC of £47,533 per QALY when all SAEs are excluded from the analysis.

A range of additional univariate sensitivity analyses explored the effects of applying the manufacturer clinical estimates and cost estimates within the model, the rates of discontinuations assumed for active treatments, the assumed step change in utility for an SRE naïve patient experiencing an SRE, applying utility multipliers for those nearing death, limiting or excluding the effects of SAEs, altering the time horizon to five years and to two years, excluding general mortality and extending the effect of spinal cord compression to beyond 5 months from diagnosis.

As would be anticipated, excluding the step change in utility estimated between SRE naïve patients and SRE experienced patients has quite a large impact upon the results of the modelling for SRE naïve patients. This is not to say that there is no effect, only that aspects of the cancers other than just SREs may be contributing to this, particularly if SRE naïve patients tend to be earlier in the disease pathway than SRE experienced patients.

The other aspect that may have an impact is the treatment of spinal cord compressions. Extending the average quality of life decrement measured in the five months subsequent to the compression through to death improves the estimated cost effectiveness, particularly among SRE naïve prostate cancer patients. This has to be read in conjunction with the above comment on the change in utility estimated between SRE naïve patients and SRE experienced

patients. But this average decrement being applied through to death improves the cost effectiveness of denosumab among SRE naïve prostate cancer patients from £69,510 per QALY to £51,655 per QALY compared to BSC. Applying the maximum decrement rather than the average further improves it to £43,905 per QALY. But applying these within the analyses that also apply the SRE subgroup specific hazards only improves it to £81,273 per QALY for the average decrement and to £67,508 per QALY for the maximum decrement.
There is limited data on the rates of paralysis from spinal cord compression and the cost estimates from averaging reference costs may be too low. CG75 suggests an average therapy cost of £14,173 [£13,705]. Adding this to the average rehabilitation costs and applying the average decrement through to death results in a cost effectiveness estimate for SRE naïve prostate patients of [redacted] per QALY compared to BSC, and [redacted] per QALY for the maximum decrement. But within the analyses that apply the SRE subgroup specific hazards the estimates rise to [redacted] per QALY and [redacted] respectively.

Probabilistic modelling suggests that within the usual range of cost effectiveness thresholds there is relatively little uncertainty around the cost effectiveness acceptability frontier. The central estimates are also in line with those of the deterministic analyses.

**Discussion**

***Strengths, limitations of the analyses and uncertainties***

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. In terms of limitations, non-English language studies were excluded. Only subgroup data were available for denosumab for NSCLC, and other solid tumours excluding NSCLC. 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.

In terms of 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.
- Pathological fractures vary from unnoticeable, asymptomatic fractures to vertebral fractures associated with spinal cord compression that result in paraplegia. The skeletal survey frequency in the denosumab RCTs is unlikely to be the case in clinical practice

and more frequent tests may have resulted in asymptomatic pathological fractures being detected that would have remained undetected in clinical practice until they became symptomatic. In addition, in the RCTs once a SRE had been detected and classified as asymptomatic it could not later be reclassified as symptomatic – this could potentially lead to a rate of symptomatic SREs detected that was lower than that observed in clinical practice.

- More than one SRE may occur in relation to a single event. In order to provide an estimate of the number of SRE events rather than just the overall number of SREs, in the denosumab and bisphosphonate trials a subsequent SRE was counted as a separate SRE only after a defined period (usually 21 days). 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.

The assessment group economic analysis is in part framed by the manufacturer analysis in terms of outlook and approach. The cost utility modelling relies upon it for the greater part of its input, due to a paucity of other data sources for elements such as quality of life values. But the broad conclusions of the assessment appear relatively insensitive to the approach adopted, as shown by the much simpler within trial analyses.

Several questions remain concerning the underlying assumptions:

- 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?
- To what extent does the available data on SRE naïve patients and SRE experienced patients reflect the likely patient groups for whom zoledronic acid is used? 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?
- 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 zoledronic acid would be sufficient to make denosumab not cost effective when judged by conventional thresholds.

***Generalisability of the findings***

The three RCTs comparing denosumab with zoledronic acid were large, international, multi-centre trials. The participants all had advanced cancer (breast, prostate, lung or other solid tumours) with ≥ 1 bone metastases, ECOG status ≤ 2 and a life expectancy of ≥ 6 months. Therefore it is reasonable to expect that the results of the trials would be generalisable to patients meeting the above criteria, although not to patients with a life expectancy of < 6 months.

[redacted] Patients with poor renal function (creatinine clearance < 30ml/minute) were excluded from the trials on the basis that they could not be randomised to zoledronic acid as the drug would be contraindicated for them. Therefore the effects of denosumab on patients with advanced cancer with bone metastases and poor renal function are unknown. The RCT for other solid tumours (excluding breast or prostate) analysed a number of different types of solid tumour together as it would not be practical to conduct sufficiently powered trials on each tumour type. However this makes it difficult to assess whether denosumab is more effective in one type of tumour than another.

**Conclusions**

***Implications for service provision***

Compared with zoledronic acid and BSC, denosumab is effective in delaying time to first on-study SRE and reducing the risk of multiple SREs. These results are mostly statistically significant and met the minimally clinically significant change described by clinical experts (delay of more than three months or HR reduction of more than 20%). However the importance of the composite SRE outcome, and spectrum of corresponding possible health states, to an individual patient is not clear. Evidence for the effectiveness of denosumab compared with zoledronic acid in reducing pain and improving relative quality of life is less evident. The NMA results indirectly comparing denosumab with BSC are subject to considerable uncertainty and should be interpreted with caution.

Any change in the treatment pathway of patients with bone metastases is likely to have implications for service provision. The impact of denosumab depends on whether the patient would alternatively have received an intravenous or oral bisphosphonate, or BSC. Compared with intravenous delivery, subcutaneous injections would require a shorter time to administer. For those receiving an intravenous bisphosphonate, as denosumab is given by injection it could potentially be given to some patients in an outpatient setting, GP surgery or even at

home by a district nurse or other qualified healthcare provider. However such a shift may require additional resources and training in the community. For patients who would have previously been treated with BSC alone, the addition of denosumab would usually mean additional healthcare appointments.

The manufacturer model, the assessment group within trials analyses and the assessment group cost utility model all estimate denosumab to result in patient benefits from reduced SREs compared to zoledronic acid, and larger benefits compared to best supportive care. But the estimates of the numbers of SREs avoided per patient are small, when compared to zoledronic acid typically less than 0.3 SREs over the patient lifetime and often a lot less than this. Spinal cord compression is relatively rare. The QALY gains from the number of SREs avoided compared to zoledronic acid are small, typically less than 0.02 QALYs over the patient lifetime and again often quite a lot less than this.

[redacted]

Given this and the small QALY gains, denosumab is in the main estimated to dominate or be cost effective compared to zoledronic acid. But zoledronic acid comes off patent quite soon. Only a relatively minor price reduction of [redacted] or less for zoledronic acid is required to result in the additional net costs from denosumab rendering it not cost effective at current thresholds.

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.

***Suggested research priorities***

Further research would be helpful in the following areas:

- The effectiveness of denosumab compared with zoledronic acid in delaying time to first SRE and reducing the risk of first-and-subsequent SREs in patients with hormone-refractory prostate cancer and painful bone metastases for whom other treatments have failed.
- Whether there is an identifiable subgroup of patients at higher risk of spinal cord compression for whom denosumab might result in larger QALY gains.

- The safety and efficacy of denosumab in (i) patients with severe renal impairment and advanced cancer (breast, prostate, non-small cell lung and other solid tumours) and (ii) patients with advanced cancer who have previously been exposed to a bisphosphonate.
- The role of bone markers in identifying subgroups of patients with advanced cancer and bone metastases who may be likely to benefit from bone targeting therapies.
- Given the NSCLC subgroup result, further exploration of the effectiveness of denosumab compared with zoledronic acid for overall survival in patients with NSCLC and bone metastases.

# 3 BACKGROUND

## 3.1 Description of health problem

### *3.1.1 Brief statement describing health problem*

Cancer is the leading cause of death in females and the second commonest cause of death in males; almost 30% of all deaths in England and Wales are caused by cancer.[1] Breast, prostate, lung and colorectal cancer are the commonest causes of cancer death in the UK.[2] In most cases, death is not caused by the primary tumour but by metastases or their complications. Almost any cancer can metastasise to bone, but cancers of the breast, prostate, lung, bladder, thyroid and kidney spread to bone most often. Cancer disrupts the architecture of bone causing structural weakness. Subsequently patients may suffer severe bone pain, pathological fractures or spinal cord compression; further reducing quality of life and adding to the burden of disease. Treatments which alleviate, prevent or delay these events offer the possibility of improving a patient's quality of life.

### *3.1.2 Overview of types of cancer commonly spreading to bone*

*Breast cancer*

Bone metastases and their consequences depend on the type of primary tumour. Breast cancer is the commonest cancer in women. In the UK approximately 124 women per 100,000 are diagnosed with breast cancer each year.[2] Approximately 0.5% of women have bone metastases at diagnosis; with 4.7% developing bone metastases in five years.[3] Bone metastases are associated with reduced median survival of approximately 24 months and five year survival of 20%.[4] However, survival is more heavily dependent on the presence of visceral organ metastases. Breast cancer commonly spreads to bone, liver, lung and brain. It has been estimated that breast cancer patients with metastatic disease only to bone survive six months longer than those with bone metastases and metastases outside a bone (1.6 years compared with 2.1 years).[5]

Breast cancer most commonly originates from cells lining ducts or lobules (namely ductal carcinoma or lobular carcinoma). The natural history of the tumour is dependent on a range of different variables which, in turn, contribute to classification. TNM is the most important prognostic classification and refers to the size of the tumour (T), spread to lymph nodes (N) and presence of metastases (M). Low grade or pre-cancerous cells are referred to as *in-situ* carcinoma and do not cause metastases, unless the tumour progresses to an invasive carcinoma. Tumour aggressiveness can be predicted by the degree to which tumour cells are differentiated; poorly differentiated cells tend to be more aggressive, whereas well differentiated cells are less so. Treatment and prognosis depend on receptors expressed by tumour cells. The three most important are oestrogen receptor (ER), progesterone receptor

(PR) and Human Epidermal Growth factor receptor 2 (HER-2). Generally tumours which are receptor negative are less responsive to treatment and have a worse prognosis.

*Prostate cancer*

In men the commonest cancer is prostate cancer. Approximately 98 men per 100,000 are diagnosed with prostate cancer in the UK each year. Almost 24 men per 100,000 each year die because of prostate cancer.[2] Prostate cancer often progresses to involve bone. At diagnosis 22% of patients have stage IV disease and a further 25% will develop clinically detectable metastases over the course of the disease.[6] One study found that 90% of patients with prostate cancer had some evidence of bone involvement at death.[7] Survival is reduced considerably with the presence of bone metastases and five year survival drops from 56% in patients without bone metastases to 3% in patients with bone metastases.[8] However this does not imply that bone metastases cause death *per se*, but rather more aggressive cancer.

Prostate cancer originates in glandular cells and is therefore categorised as an adenocarcinoma. Similar to breast cancer, the TNM classification is the most important prognostic indicator. A worse prognosis is associated with the presence of disease in lymph nodes, or beyond. The grade of tumour cells is measured using the Gleason score. A high Gleason score suggests a poorly differentiated tumour and therefore poorer prognosis. Prostate specific antigen (PSA) is a protein released by the prostate and can be a marker for cancer. However there has been much debate around PSA testing. High levels of PSA can be found in patients without cancer and normal levels can be found in patients with cancer.[9] Prostate tumours are dependent on androgen in order to progress. Therefore anti-androgen treatment can delay progression; by either chemical or surgical castration. When tumours respond to castration therapy they are classified as castration-sensitive prostate cancer (CSPC), and when tumours no longer respond to castration treatment they are classified as castration-resistant prostate cancer (CRPC). Hormone-sensitive and hormone-refractory nomenclature has been used. However some tumours remain dependent on androgens (and amenable to further androgen deprivation)[10] to progress irrespective of castration therapy, the term castration-resistant is more accurate.

*Lung cancer*

Lung cancer is the second commonest cancer, after breast (females) and prostate (males), and has an incidence of 48 per 100,000 per year. Lung cancer prognosis is very poor. More people die from lung cancer each year than any other cancer (40 patients per 100,000).[2] One year survival is 25% (males) and 26% (females). Five-year survival is only 7.8% (males) and 8.7% (females) and reflects early detected cancers at a surgically resectable stage.[11] Spread of

tumour to bone is common in lung cancer. Up to 36% of patients with lung cancer have evidence of bone metastases at death.[12] Other organs to which lung cancer often metastasises include the adrenal glands and the brain.

Classification of lung cancer is histological. Non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) comprise more than 95% of all lung cancers. NSCLC includes squamous cell carcinoma, adenocarcinoma and large-cell carcinoma. SCLC carries a worse prognosis and metastases are usually present at diagnosis. Both SCLC and NSCLC are staged using the TNM classification, or categorised as stage IA (better prognosis) to IV (worse prognosis).

*Other solid tumours*

Almost any cancer can metastasise to bone. At autopsy 35-42% of thyroid, renal and bladder tumours have evidence of bone metastases.[13] Colorectal cancer mainly spreads to the liver but in 6-10% of cases metastasise to bone.[14,15] Since colorectal cancer is the third commonest cancer, after breast (females), prostate (males) and lung, the actual number of patients with bone involvement is considerable. Each cancer has different sub-classifications, each with their own pathophysiology, treatment and prognosis. For example papillary thyroid cancer has a very good prognosis compared to anaplastic thyroid cancer. Bladder tumours may be superficial requiring only local ablation therapy, or may be muscle invasive requiring surgical resection or radical radiotherapy to the bladder. Therefore the pathway to bone metastases in each cancer type varies according to primary site, cell type, classification and anti-neoplastic treatment.

### *3.1.3 Pathophysiology of bone metastasis*

Bone provides an ideal environment for adhesive tumour cells; illustrated by the "seed and soil hypothesis".[16] Blood flow through bone marrow provides ample opportunity for transportation of "seeds" (tumour cells). A range of growth factors provides suitable "soil". Once tumour cells have been established in bone marrow the normal physiology of bone remodelling is disrupted.

Normal bone remodelling is dependent on the balance between osteoblasts and osteoclasts on the trabecular surfaces. Osteoblasts arise from mesenchymal stem cells and are responsible for bone formation. A cascade of bone proteins and growth factors drive and halt the bone formation process.

Osteoclasts resorb bone. They derive from the monocyte-macrophage lineage and rely on various cytokines and osteoblastic products to develop. One such cytokine is a tumour

necrosis factor called receptor activator of nuclear factor-κB ligand (RANKL). Through increased expression of RANKL, osteoclasts are induced and therefore bone resorption increases. Bone resorption results in calcium release. When combined with increased calcium reabsorption in the kidneys, this can lead to hypercalcaemia of malignancy (HCM).

Bone metastases result in an imbalance of osteoclast and osteoblast activity. If osteoclasts are primarily activated, bone resorption increases and metastases are more lytic in nature. Osteolytic lesions are thin lesions due to the active resportion of bone and can be detected on plain radiograph. Appearance can be from a single well defined lesion to multiple ill-defined lesions.

If osteoblasts are activated, bone formation increases and bone metastases are more sclerotic in nature. Since sclerotic lesions are caused by increased bone formation, these lesions tend to be denser. The fact that these lesions are denser does not result in normal/increased bone strength, but rather weakness because of disruption of the bone matrix. Therefore any imbalance of osteoblasts or osteoclasts causes disruption of the essential bone architecture and results in bone weakness.

Traditionally it was thought that bone metastases could be osteolytic, osteoblastic or mixed. Prostate cancer generally results in predominately osteoblastic lesions and breast cancer predominately osteolytic lesions.[17] However current opinion is that a spectrum exists with no metastasis being purely osteolytic or osteoblastic.[18]

### *3.1.4 Clinical sequelae of bone metastases*

The impact of bone metastases on patients is considerable. Bone metastases are associated with a worse prognosis, reduced quality of life and increased risk of complications. Quality of life is decreased by bone pain, reduced mobility and complications such as pathological fracture, spinal cord compression and HCM. Metastatic bone pain can be of a constant or intermittent nature and it is not unusual for strong opioid analgesics to provide little relief. Alternatives to first line analgesics include radiotherapy, bisphosphonates, corticosteroids or radionucleotides. Mobility may be reduced because of bone pain and other complications. Immobility places individuals at risk of other complications such as thromboembolism and lower respiratory tract infection; further increasing morbidity.

Complications are caused by weakness in the bone or disrupted calcium homoeostasis. Either osteoblastic or osteolytic lesions can cause pathological fractures; defined as pathological because minimal or no force is required. The commonest sites for fractures are the axial

skeleton and long bones. Vertebral body collapse is common and can cause deformity of the spine. Saad and colleagues[19] demonstrated that pathological fractures were correlated with reduced survival. Surgical fixation or radiotherapy can be used to prevent or treat pathological fractures.

The most serious complication of bone metastasis is spinal cord compression (SCC). Impingement of the spinal cord (SCC) is caused by either vertebral body collapse or direct tumour growth into the spinal canal. Even with emergency treatment, SCC can cause irreversible neurological damage, paraplegia and death. Neurological damage can range from mild sensory loss to complete paraplegia with loss of bowel and bladder function.

A further serious complication of bone metastases is hypercalcaemia (HCM). High circulating levels of calcium are caused by release of calcium from metastases and dysregulation in the kidney. HCM causes a typical pattern of unpleasant, non-specific symptoms. Untreated it can lead to coma, cardiac arrhythmias and death.

The term 'skeletal related events' (SRE) is used to group the following complications together for research purposes; pathological fracture, spinal cord compression, and radiotherapy or surgery to bone. Some definitions include hypercalcaemia or change in anti-neoplastic therapies. The marketing authorisation for denosumab defines the term SRE as pathological fracture, spinal cord compression, and radiation to bone or surgery to bone. SREs should be considered as a spectrum of conditions; from unnoticed asymptomatic fractures to spinal cord compression resulting in paralysis.

Brown and colleagues,[20] using RCT data, investigated baseline prognostic factors for patients experiencing an SRE. They found significant factors included age, pain score, prior history of SRE, lesion type (osteolytic, osteoblastic or mixed) and elevated bone specific alkaline phosphatase (BSAP) or lactate dehydrogenase (LDH). Bone pain at diagnosis has also been associated with increased SRE risk.[21] The incidence of SREs in patients with bone metastases without prior bisphosphonate treatment was 3.5 events per year.[22] Sathiakumar and colleagues,[23] using Medicare linked data, found increased risk of death in patients with bone metastases from prostate cancer plus an SRE compared with patients with bone metastases plus no SRE. Yong and colleagues[24] found a similar result in breast cancer. However the majority of trials of bone modifying agents aimed at delaying SREs in patients with bone metastases have not been shown to affect overall survival.

In addition, bone metastases have wider implications for patients. Aside from the symptoms and complications, the diagnosis of bone metastases substantially increases healthcare contact. Patients may require a change in anti-neoplastic medications, careful titration of analgesics, radiotherapy, intravenous bisphosphonates, radiological imaging or frequent blood tests. Increased healthcare appointments can be especially difficult for patients who live in rural locations or have poor transport. Bone pain, decreased mobility and SREs undoubtedly have a further impact on patients and their families. Bone pain is characteristically severe and can be difficult to control. SREs can result in length hospital stays and reduced mobility, especially in the case of communicated pathological fractures or spinal cord compression. The combination of increased contact with healthcare, reduced mobility and increased pain inevitably restricts daily activities and results in patients requiring a higher level of care. Increased care has a subsequent impact on carers and social services.

### *3.1.5 Measurement of disease*

*Investigations for bone metastases and SREs*

Bone metastases and SREs can be measured in several different ways.[25] At the time of cancer diagnosis clinicians may screen for metastases. The decision to screen depends on stage of tumour and patients' symptoms. Skeletal scintigraphy (bone scan) uses injected radioactive material, which is then scanned with a gamma camera. Areas of increased bone metabolism are shown. This test shows the whole skeleton and is advantageous for a broad examination of the skeleton in asymptomatic patients. Plain radiographs (x-rays) are used for investigation of specific bones where metastases are suspected. Other investigations can then be used to investigate bone lesions, such as computerised tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and single-photon-emission CT (SPECT).

Bone markers, measured in blood or urine, have been used to monitor bone turnover in clinical trials. Patients with bone metastases and elevated bone markers have increase risk of SREs.[26] It has been suggested that bone markers could be used to stratify risk of SRE in individuals with bone metastases; assisting in the choice of bone-modifying agents and monitoring treatment response.[27,28] There are several different bone markers, including BSAP, osteocalcin and N-terminal type 1 procollagen peptides (PINP) markers for monitoring bone formation, and CTX and NTX for monitoring bone resorption. Denosumab trials have included measures of NTX and BSAP as secondary outcomes.[29-31] N-terminal propeptide of type 1 collagen (NTX) increases in response to osteoclast-mediated bone resorption and can be measured in the blood or urine. During bisphosphonate treatment, normalised levels of

NTX appear to be associated with a reduced risk of SREs.[32,33] BSAP reflects osteoblastic activity by measuring bone formation. Bisphosphonate and denosumab treatment have been found to reduce BSAP. Conversely persistent elevation of BSAP despite bisphosphonate treatment is associated with increased SREs.[32] American Society of Clinical Oncology guidelines do not recommend the use of bone markers outside the trial setting.[34]

In routine clinical practice acute uncomplicated pathological fractures are generally investigated by plain radiographs. In the trial setting regular skeletal surveys have been used to screen and diagnose pathological fractures. A skeletal survey is performed by taking plain radiographs of skull, chest, spine, pelvis and long bones of the arms and legs. Therefore both asymptomatic (lesions demonstrated radiologically but the patient does not complain of any symptoms) and symptomatic fractures will be observed. For pathological fractures of the spine, plain radiographs may not be sufficient. There may be uncertainty about the presence of a fracture and plain radiographs do not assess the integrity of the spinal canal. In this scenario, imaging with a MRI or CT scan may be necessary. In the case of suspected spinal cord compression MRI is the investigation of choice.

Hypercalcaemia often presents with non-specific symptoms and is easily diagnosed on blood test. Signs and symptoms worsen as serum calcium increases. A serum calcium of more than 2.6 mmol/l is suggestive of hypercalcaemia.

*Measuring SRE*

There are several ways of recording SRE data in clinical trials;

- Time to first SRE
- Time to first and subsequent SREs (multiple event analysis)
- SRE incidence
- Proportion of patient with at least one on-study SRE
- Skeletal Morbidity Rate (SMR) – number of events per year
- Skeletal morbidity period rate (SMPR) – the number of 12-week periods with new SREs divided by the total observational time

It is important to note that SRE as a composite end point includes both complications of bone metastases (pathological fracture and SCC) and therapeutic or preventative measures (radiotherapy and surgery). Caution is needed since radiotherapy and surgery would be considered best supportive care.[35,36] Therefore measures of radiotherapy and surgery contribute to both the treatment and outcome measure.

Trinkaus and colleagues[37] compared observational SRE frequency in "real life" with SRE frequency in the IV bisphosphonate trials. They found a higher rate of SREs in the trial setting compared to "real life". This may reflect frequent bone scan which are undertaken in trials.

The various methods of assessing SRE data have evolved to overcome specific problems.

Some outcomes, such as proportion of patients with at least one on-study SRE or SMR, fail to consider time delays in SREs. For example, an individual who suffers spinal cord compression on day 1 of a trial is considered equivalent to an individual who suffers spinal cord compression after a year. To overcome this issue time-to-first SRE can be measured. This outcome does not distinguish the number or timing of subsequent SREs. Consequently the multiple event analysis was developed.[38] The Andersen-Gill system is the commonest method used for multiple event analysis. It includes a measure of both time and number of events. This method has been criticised because it fails to differentiate between individuals who have died and individuals who have left the trial for another reason.[39] Other methods have been described which also attempt to take mortality into account.[40,41]

The choice of SRE measure depends on what is considered the most important outcome. To measure SRE prevention, the proportion of patients experiencing an SRE would be more suitable. To measure a reduction in rate, SMR/SMPR would be most appropriate. However to measure delay, time-to-first or time-to-first and subsequent SRE would be more appropriate.

The situation is made more complex as more than one SRE may occur in relation to a single event and therefore the second SRE is dependent on the first. For example an individual may suffer a pathological fracture, which is treated by radiotherapy or surgery (two SREs). In the pivotal denosumab and bisphosphonate trials a subsequent SRE is counted only after a 21 day period. This is not the case for SMR, which assumes independence for each event and can therefore lead to multiple counting of events. In an attempt to address this issue the SMPR outcome has been used.

SRE incidence is generally not considered appropriate due to underestimation of time variability within the data (similar criticism could be made of SMR).[42] A patient who suffers several SREs within the first 6 months is considered equivalent to a patient who suffers the same number of events over several years. The former patient is likely to have a reduced quality of life compared with the latter.

Trials have consistently used SRE as a composite outcome. Undoubtedly this increases efficiency and power, however some caution is needed. However the impact on healthcare resources and a patient's quality of life is vastly different for spinal cord compression compared with an asymptomatic rib fracture. Neither does this SRE composite outcome directly measure factors important to patients such as mobility or pain (these are measured indirectly through need for radiotherapy or surgery).[43]

#### *3.1.6 Burden of bone metastases and SREs on healthcare and society*

Undoubtedly bone metastases and SREs require considerable healthcare resources. In 2010 Pockett and colleagues,[44] reported the hospital burden associated with bone metastases and SREs from breast, prostate and lung cancer in Spain. They collected data on over 28000 patients over one year. The incidence of hospital admission was greatly increased when an SRE occurred. In breast cancer the hospital admission incidence rate was 95 per 1000 patients over three years for non-SRE related metastatic bone disease and 211 per 1000 for SRE-related admissions. In lung and prostate cancer the incidence was 156 (lung) and 163 per 1000 patients (prostate) over three years for non-SRE related metastatic bone disease and 260 and 150 for an SRE-related admission respectively.

### 3.2 Current service provision

#### *3.2.1 Current management of bone metastases and SREs*

There are four NICE guidelines relevant to this appraisal

- Breast cancer (CG81[45])
- Prostate cancer (CG58[46])
- Metastatic spinal cord compression (CG75[47])
- Lung cancer (CG121[48])

These guidelines recommend the use of bisphosphonates (BP) in:

1) All patients with advanced breast cancer and newly diagnosed bone metastases,[45]
2) Patients with 'hormone resistant' prostate cancer and painful bone metastases when other treatments (including analgesics and palliative radiotherapy) have failed[46] and
3) Patients with breast cancer or multiple myeloma, plus vertebral involvement to reduce pain and prevent complications.[47]

Bisphosphonates are not currently recommended to prevent skeletal complications in prostate cancer[46] or tumours with vertebral involvement, excluding breast and multiple myeloma.[47]

The lung cancer guideline[48] states "methods of treating bone metastases include radiotherapy, bisphosphonates and nerve blocks"[49] and "the effect of bisphosphonates…needs more research".[50]

The American Society of Clinical Oncology (ASCO) has recent published guidelines concerning the use of bone-modifying agents in metastatic breast cancer. Based on clinical efficacy, not cost effectiveness, ASCO has recommended the use of zoledronic acid, pamidronate sodium or denosumab in patients with bone metastases from breast cancer.

The Scottish Intercollegiate Guidelines Network (SIGN) suggests that there was insufficient evidence to recommend bisphosphonates for first line treatment of cancer-related pain, but do recommend that bisphosphonates should be considered.[51] The SIGN breast cancer guideline[52] recommends bisphosphonates in patients with metastatic breast cancer and symptomatic bone metastases.

An expert panel of European clinical oncologists has published recommendations.[53] Based on clinical effectiveness, but without economic evaluation, they recommended that all patients with bone metastases from lung cancer should be prescribed a bisphosphonate.

*Bisphosphonates*

Bisphosphonates reduce bone resorption by inhibiting osteoclasts.[54] Clinical effectiveness starts after 6-12 months of treatment.[55] There are first, second and third generation bisphosphonates. Early non-aminobisphosphonates include clodronate and etidronate. The addition of a nitrogen group to the bisphosphonate structure was found to increase potency by inhibition of the HMG-CoA reductase pathway. These aminobisphosphonates include ibandronic acid, pamidronate and zoledronic acid.

During the early studies of oral nitrogen containing bisphosphonates, an association with oesophagitis was frequently reported.[56] Therefore zoledronic acid and pamidronate are only available as intravenous preparations. Ibandronic acid is available as an oral or intravenous preparation. Intravenous bisphosphonates are excreted rapidly from the kidneys and are typically associated with a higher incidence of hypocalcaemia and renal impairment compared with oral bisphosphonates.[57] Administration time varies from 15 minutes for zoledronic acid and 120 minutes for pamidronate.

Oral bisphosphonates are absorbed by passive diffusion in the gastrointestinal tract. As a result less than 6% of the active compound is absorbed and this is further reduced with the

presence of food. In addition, oral bisphosphonates increase the risk of oesophageal erosions, inflammation and neoplasm.[58] It is therefore recommended that patients remain upright for 30-60 minutes after ingestion. Consequently oral bisphosphonates become burdensome for patients.[59] Location of treatment is important to patients. One study found that patients prefer administration at home but this is not often possible with intravenous treatments.[60]

Bisphosphonates are considered to be relatively safe drugs. Possible adverse reactions include renal failure, osteonecrosis of the jaw, hypocalcaemia and acute phase reaction. To avoid renal impairment, renal function is checked before administration, dose adjusted if necessary and the IV infusion is given slowly. McDermott and colleagues[61] assessed predictors of renal impairment in patients given zoledronic acid. The following predictive factors were found on multivariate analysis; age, myeloma or renal cell cancer, number of doses, concominant NSAID therapy and current or prior treatment with cisplatin. Osteonecrosis of the jaw (ONJ) has only recently been associated with bisphosphonates.[62] ONJ leads to oral or periodontal lesions which are usually associated with previous dental procedures. Hypocalcaemia can be rectified with oral calcium. Acute phase reaction usually presents with transient pyrexia following first administration.

Four bisphosphonates are currently licensed in the UK for bone metastases;

a) Zoledronic acid (Zometa™, Novartis) is licensed for the reduction of bone damage in advanced malignancies involving bone. It is administered by intravenous infusion over at least 15 minutes at a dose of 4 mg every 3-4 weeks.
b) Disodium pamidronate (Aredia, Novartis) is licensed for osteolytic lesions and bone pain in bone metastases associated with breast cancer or multiple myeloma. It is administered by slow intravenous infusion (over at least 2 hours) at a dose of 90 mg every 4 weeks.
c) Sodium clodronate (Bonefos™, Bayer Schering; Clasteon™, Beacon; Loron 520™, Roche) is licensed for osteolytic lesions, hypercalcaemia and bone pain associated with skeletal metastases in patients with breast cancer or multiple myeloma. It is administered by mouth at a dose of 1.6-3.2 grams daily.
d) Ibandronic acid (Bondronate™, Roche) is licensed for the reduction of bone damage in bone metastases in breast cancer. It is administered either by mouth (50 mg daily) or intravenous infusion (6 mg every 3-4 weeks).

Therefore zoledronic acid is the only drug licensed for cancer involving bone, other than breast or multiple myeloma. Zoledronic acid has been the most studied bisphosphonate and, according to expert opinion, is the most widely used bisphosphonate. The patent for

zoledronic acid is expected to expire in 2013. There are currently no firm criteria to advise when bisphosphonates should be stopped.

*Best supportive care*

Best supportive care varies between each primary cancer type.

In breast cancer with bone metastases best supportive care encompasses the use of bisphosphonates to prevent skeletal-related events and reduce pain. However for the purpose of this report the definition of best supportive care does not include bisphosphonates. Pain is also managed by the use of both simple and opioid analgesics, corticosteroids and non-steroidal anti-inflammatory agents. External beam radiotherapy is used to control pain at specific sites and, less commonly now, systemic radiopharmaceuticals may be used for widespread pain at multiple sites not controlled by other means. All patients with metastases in a long bone should be assessed for the risk of pathological fracture and referred to an orthopaedic surgeon for consideration of prophylactic fixation. Not all patients will require treatment with all modalities discussed above. NICE guidelines currently recommend that all patients with bone metastases receive a bisphosphonate whilst ASCO guidelines recommend the use of a bone modifying agent in patients with bone metastases and evidence of bone destruction. There is variation in the use of the other interventions mentioned dependent on local practice and patient factors.

In castration-resistant prostate cancer with bone metastases current best supportive care (BSC) encompasses the use of systemic anti-cancer therapies including chemotherapy and further hormone therapies. Palliative external beam radiotherapy, and systemic radionucleotides, such as Strontium-89, are widely used and may be used on multiple occasions to treat metastatic bone pain. Despite these measures, pain may continue to be burdensome and analgesics, often requiring specialist pain services, are frequently required. Attitudes to systemic anti-cancer therapies used in this context vary across the UK, in particular there remains widespread controversy about the optimal timing of docetaxel-based chemotherapy, some clinicians opting to use it to prevent symptoms such as bone pain, others saving it until symptoms become burdensome. Two new drugs, cabazitaxel and abiraterone acetate, which are licensed in this indication, may change BSC patterns in this population, but neither drug has been the subject of published NICE review and access outside of clinical trials remains limited in the UK. The treatment of SRE is similar to other solid tumours. Pathological fractures can be treated or prevented with surgery, radiotherapy or analgesics. Current practice is that bisphosphonates are not given to prevent complications of bone metastases, such as pathological fractures and spinal cord compression. However bisphosphonates are used to treat pain when first line analgesics have not alleviated pain.

In lung cancer with bone metastases best supportive care may include chemotherapy, palliative radiotherapy, antibiotics, steroids, surgery, analgesics and antiemetics.[63] Certain treatments are aimed at slowing disease progress (chemotherapy), whilst others at alleviating (analgesics and antiemetics) or preventing symptoms (surgery to prevent pathological fracture). Best supportive care may vary according to the location or primary tumour and presence of distal metastases. Bisphosphonates are generally not used to prevent SREs. However clinicians may consider bisphosphonates as a second line analgesic option for painful bone metastases. Best supportive care for pathological fracture and spinal cord compression in lung cancer is similar to other solid tumours.

*Current treatments of SREs*

Treatment of pathological fractures depends on the severity of injury, bones involved and degree of destruction. Management options include analgesics, immobilization, surgical fixation, radiotherapy or a combination of the above. The impact to patients of pathological fractures varies from unnoticed asymptomatic fractures to vertebral fractures associated with spinal cord compression and paraplegia.

Management of spinal cord compression has been described in Metastatic Spinal Cord Compression.[47] The guidelines highlight the need for early diagnosis and imaging with MRI. Acute treatment recommendations include good nursing care, corticosteroids and appropriate case selection for surgery or radiotherapy. Moreover the guidelines make recommendations for long term care, including management of pressure ulcers, bladder or bowel incontinence, postural hypotension and lung secretions, prevention of thromboprophylaxis and planning for rehabilitation or long term care.

Hypercalcaemia of malignancy (HCM) can present with various different signs and symptoms. If untreated, HCM can lead to confusion, drowsiness or coma. Rehydration and bisphosphonate treatment are the cornerstone of management. Loop diuretics and steroids can also be used. Older agents such as plicamycin, calcitonin and gallium nitrate are not commonly administered.

*Variation in service*

There is variation amongst oncologists in the choice of bisphosphonates and more so in breast cancer where four bisphosphonates are licensed. With no clear guidelines about which bisphosphonate to use, the decision is often made by the individual clinician. Based on expert opinion zoledronic acid is the most widely used bisphosphonate.

Bisphosphonates are used consistently in breast cancer; however the use of bisphosphonates in other cancers varies. In metastatic tumours other than breast cancer, some clinicians use bisphosphonates routinely, others reserve bisphosphonates only for uncontrolled pain and others rarely use bisphosphonates. With the imminent patent expiry of zoledronic acid and the anticipated reduction in price, patterns of use may change significantly in the near future.

Fallowfield and colleagues[64] conducted a UK survey to evaluate bisphosphonates prescribing habits amongst oncologists. They found 53% of oncologists gave IV and oral drugs, 40% only gave IV drugs and 7% gave only oral drugs. Zoledronic acid (56-85%) and pamidronate (23-42%) were the commonest IV drugs and ibandronic acid (66%) was the commonest oral bisphosphonate used. Reasons reported for using oral preparations included "health authority/primary care trust only funds oral preparation", "local guidelines dictate which patients receive oral/IV" or "IV preparations are not listed on the local formulary".

Variation in best supportive care exists between treatment centres. Local policy, available resources and clinician prescribing habits all affect the extent to which patients may be offered certain bisphosphonates, analgesics or antineoplastic medications.

### *3.2.2 Current service cost*

Bisphosphonate are an adjuvant to best supportive care. BNF62 gives a list price for zoledronic acid of £174.17 which can be administered as a 15 minute intravenous infusion. Disodium pamidronate is given a list cost of £165.00 in BNF62 and is administered as a slow intravenous injection over at least two hours every four weeks. Additional costs include staff time to administer bisphosphonates, monitoring costs, in particular renal function, and capital costs.

## 3.3 The technology

### *3.3.1 Summary of intervention and important subgroups*

Denosumab is a fully human monoclonal antibody. It has been designed to reduce osteoclast-mediated bone destruction through the inhibition of the RANKL. Tumour cells appear to increase the release of RANKL through activation of osteoblasts. RANKL in turn promotes osteoclast activity. Therefore inhibition of RANKL reduces bone destruction. Denosumab is the first monoclonal antibody developed with this mode of activity.

Denosumab (Prolia) is currently licensed for treatment of osteoporosis and bone loss caused by hormone ablation treatment in prostate cancer. Prolia is given at 60 mg every six months. Denosumab (Xgeva) for the prevention of skeletal related events in bone metastases from

solid tumours was granted marketing authorisation in July 2011. Multiple myeloma (MM) was not included within the marketing authorisation and therefore has been removed from the decision problem chapter of this report. The administration of denosumab is via a 120 mg subcutaneous injection every four weeks. Xgeva is administered using a higher dose and with more frequent dosing than Prolia.

The Food and Drug Administration in the US on November, 18, 2010 granted approval for a new indication for denosumab, to include the prevention of skeletal-related events in patients with bone metastases from solid tumours, to be marketed under a new proprietary name, Xgeva.

### *3.3.2 Current usage in the NHS*

Denosumab has only recently been granted licensing authorisation in the UK. The assessment group is unaware of any current use in clinical practice.

### *3.3.3 Anticipated costs associated with intervention*

Denosumab is a 4 weekly subcutaneous injection which can be administered in hospital while patients receive other therapy such as chemotherapy, at an outpatient appointment or potentially in primary care or through a dedicated health visitor domestic visit. The direct drug cost is £309.85 per dose. [redacted]

# 4 DEFINITION OF THE DECISION PROBLEM

This section specifies the decision problem, outlines the key issues and provides an explanation of changes made between the scope and protocol or subsequent to the protocol.

## 4.1 Decision problem

The purpose of this report is to assess the clinical and cost effectiveness of denosumab within its licensed indication for the prevention of SREs in patients with bone metastases from solid tumours. Denosumab offers an alternative treatment to bisphosphonates, or an addition to best supportive care, for the prevention of SREs.

### *4.1.1 Interventions*

| |
|---|
| *Scope: Denosumab* |
| *Protocol: Denosumab* |

The intervention is denosumab (Xgeva), administered every four weeks at a dose of 120 mg as a subcutaneous injection.

### *4.1.2 Population including sub-groups*

| |
|---|
| *Scope: Adults with bone metastases from solid tumours and adults with multiple myeloma* |
| *Protocol: Adults with bone metastases from solid tumours and bone disease in multiple myeloma* |

The population assessed is adults with bone metastases from solid tumours. The scope requested that each tumour type be presented separately. Breast, prostate and NSCLC are the tumours that most commonly metastasise to bone. This grouping is reflected in the published literature. Therefore the population is divided into those with breast, prostate, NSCLC and other solid tumours.

As far as the evidence allows, a sub-group based on prior history of SRE is considered.

Multiple myeloma is not included in the marketing authorisation for denosumab and has therefore been withdrawn from the decision problem.

### *4.1.3 Relevant comparators*

*Scope:*

- *Bisphosphonates such as sodium clodronate, disodium pamidronate, ibandronic acid and zoledronic acid*
- *Best supportive care*

*Protocol:*

- *Breast cancer - bisphosphonates*
- *Prostate cancer, lung cancer and other solid tumours – bisphosphonates and best supportive care*

Denosumab is compared with bisphosphonates and best supportive care.

The comparator of best supportive care is not mutually exclusive with denosumab or bisphosphonate treatment. Both on-study and in "real life" patients receive best supportive care, irrespective of denosumab or bisphosphonate treatment. Therefore a more accurate description of the comparators would be denosumab plus best supportive care compared with bisphosphonates plus best supportive care or best supportive care alone. However for the purpose of this report the terms denosumab, bisphosphonates and best supportive care are used.

In breast cancer, denosumab is compared with bisphosphonates. Denosumab is compared with zoledronic acid, disodium pamidronate, ibandronic acid and sodium clodronate, depending on available literature.

In prostate cancer the NICE guideline[46] recommends the use of bisphosphonates when conventional analgesics fail. Zoledronic acid is the only bisphosphonate licensed and is the most commonly used. Therefore denosumab is compared with best supportive care and zoledronic acid.

In NSCLC cancer the NICE guideline[48] states that, "methods of treating bone metastases include radiotherapy, bisphosphonates and nerve blocks". No clear guidance exists about when bisphosphonates should be administered. Zoledronic acid is the only bisphosphonate licensed. Therefore in NSCLC denosumab is compared with best supportive care and zoledronic acid.

In other solid tumours, excluding breast, prostate and NSCLC, no clear guidance exists about the circumstances under which bisphosphonates should be administered. Zoledronic acid is the only bisphosphonate licensed. Therefore denosumab is compared with best supportive care and zoledronic acid.

In patients with bone metastases from solid tumours who are eligible for a bisphosphonate but are contra-indicated (e.g. due to renal impairment), denosumab is compared with best supportive care.

The metastatic spinal cord compression NICE guideline[47] recommends the use of bisphosphonates in 1) breast cancer to reduce pain and the risk of vertebral fracture/collapse and 2) prostate cancer to reduce pain if conventional analgesics fail to control pain. The guideline recommends that bisphosophonates are not used to treat pain, or with the intention of preventing MSCC, in patients with vertebral involvement from solid tumour types other than breast and prostate cancer.

There is wide variation in the use of bisphosphonates for the management of patients with bone metastases in the UK. Patterns of use depend upon local and national guidelines, and physician and patient preferences. Expert opinion is used to assess the use of unlicensed bisphosphonates in solid tumours other than breast cancer.

#### *4.1.4 Outcomes*

*Scope:*

*The outcome measures to be considered include:*

- *Time to first skeletal related event (pathological fracture, spinal cord compression, radiation or surgery to the bone)*
- *Time to first and subsequent skeletal related event*
- *Incidence of skeletal related events*
- *Skeletal morbidity rate*
- *Hypercalcaemia*
- *Survival*
- *Pain*
- *Health-related quality of life*
- *Adverse effects of treatment*

*Protocol:*

*As per scope*

The above outcomes are assessed according to available literature and suitability for network meta-analysis. In addition, the proportion of patients experiencing an on-study SRE is included. This outcome is synonymous with crude incidence of patients experiencing an on-study SRE.

Where the evidence allows, each type of SRE is presented separately. SRE is defined as pathological fracture, radiotherapy to bone, surgery to bone or spinal cord compression.
The use of SRE as a composite end point is discussed in chapters 3 and 13. The term SRE is used in trials but not in clinical practice. The main criticism is that SRE encompasses a wide spectrum of possible health states, from asymptomatic fractures to spinal cord compression resulting in paraplegia, and does not directly measure pain or mobility. Including treatments (radiotherapy and surgery) in addition to complications (fracture and spinal cord compression) can make results difficult to disintegrate.

According to clinical advisors, the minimal clinically significant change in time to first SRE would be three months (RT) or a 20% reduction in hazard ratio (RJ). Mathias and colleagues,[65] correlated brief pain inventory (BPI) scores and quality of life scores (EQ-5D and FACT) using data from the trial by Stopeck and colleagues[31] comparing denosumab and zoledronic acid in breast cancer with bone metastases. The authors concluded that a two point change, or more, in BPI score should be considered as clinically meaningful.

### *4.1.5 Key issues*

The place of denosumab within the treatment pathway is a crucial issue. The following possible places in the treatment pathway are considered:

- Bone metastases from <u>breast cancer</u>
  - An alternative to bisphosphonates as a first line treatment in the prevention of SREs
  - Second line treatment for patients who have an SRE on a bisphosphonate
- Bone metastases from <u>prostate, NSCLC and other solid tumours, excluding breast cancer</u>
  - An alternative to best supportive care as a first line treatment in the prevention of SREs
  - As a first line therapy for the secondary prevention of SREs in patients who have already suffered an SRE.
  - An alternative to bisphosphonates as a second line therapy for prevention of SREs in patients for who best supportive care has not proved adequate
- Bone metastases from <u>breast, prostate, NSCLC and other solid tumours</u>

- As a second line treatment in patients unable to tolerate IV bisphosphonates, or for whom they are contraindicated.

The three main challenges with this appraisal are 1) a population that includes all solid tumours, 2) widespread variation in the use of comparators and 3) limited evidence suitable for inclusion in a network meta-analysis.

Three phase III clinical trials have evaluated denosumab compared with zoledronic acid in breast cancer,[31] prostate cancer,[29] and other solid tumours (excluding breast and prostate) and multiple myeloma.[30] Breast, prostate and lung cancer are the tumours which most commonly metastasise to bone, although almost any tumour has the potential. Treatment effect could be influenced if tumour types are combined or considered separately. In this appraisal, breast, prostate and NSCLC are considered separately; all other solid tumours are combined. Furthermore at diagnosis of bone metastases patients may have been exposed to a variety of therapies. These include chemotherapy, hormonal therapy, radiotherapy or surgery. Therefore the evidence of a treatment, which is given in addition to these therapies, and in a variety of tumour types, requires careful interpretation.

Comparators include bisphosphonates and best supportive care. There has been no NICE technology appraisal for the use of bisphosphonates in bone metastases. Four NICE guidelines give recommendations on the use of bisphosphonates in advanced breast cancer,[45] prostate cancer,[46] lung cancer[48] and metastatic spinal cord compression.[47] Variation in practice exists in the use of bisphosphonates between tumour types and the choice of bisphosphonate. Although zoledronic acid is the only licensed bisphosphonate for solid tumours, other than breast cancer, other bisphosphonates may be used off license. Not only does bisphosphonate use vary but best supportive care varies between geographical region and tumour type. Therefore best supportive care is defined by clinical experts. There is no direct evidence comparing denosumab with current best supportive care. Placebo or no active treatment is used as a proxy for best supportive care. To compare denosumab with best supportive care several network meta-analyses are required. Only data which are sufficiently homogeneous, in terms of population, intervention, comparators, outcomes assessed, SRE definition and timeframe, can be included.

Other treatment effect and cost effect modifiers include:

- Symptomatic versus asymptomatic fractures
  - Pivotal denosumab studies report combined symptomatic and asymptomatic fractures. Including asymptomatic fractures may overestimate treatment effects.

- Overall survival
  - Tumours with extended survival may benefit more from denosumab
- Place of administration of denosumab
  - Community versus hospital

### 4.2 Overall aims and objectives of assessment

| |
|---|
| *Scope:*<br>*To appraise the clinical and cost effectiveness of denosumab within its licensed indication for the treatment of bone metastases from solid tumours and multiple myeloma.*<br>*Protocol:*<br>*To appraise the clinical and cost effectiveness of denosumab, within its licensed indication, for the treatment of bone metastases from solid tumours and bone disease in multiple myeloma.* |

The purpose of this review is to appraise the clinical and cost effectiveness of denosumab, within its licensed indication, for the treatment of bone metastases from solid tumours. Multiple myeloma is not included in the marketing authorisation for denosumab and has therefore been withdrawn from the decision problem. As stated above, results are presented separately based on the type of primary cancer: (a) breast cancer, (b) prostate cancer, (c) NSCLC and (d) other solid tumours excluding breast, prostate or NSCLC. Where evidence allows, data for each type of SRE (pathological fracture, requirement for radiation therapy to bone, surgery to bone, or spinal cord compression) are presented separately. In addition, where evidence allows, data on patients with a prior history of SREs are presented separately.

The following aspects are not included in the aim of this report:

- Denosumab for the prevention of bone metastases
- The clinical effectiveness and cost effectiveness of bisphosphonates relative to best supportive care

# 5 METHODS FOR REVIEWING EFFECTIVENESS

## 5.1 Identification of studies

Studies were identified by searching electronic databases and relevant websites, contact with clinical experts and the scrutiny of bibliographies of retrieved papers.

The databases searched were MEDLINE (1948 to April 2011), EMBASE (1980 to March 2011), Cochrane Library (all sections) (Issue 1, 2011), and Web of Science with Conference Proceedings (1970 to May 2011). Auto-alerts were set-up in Medline and Embase to identify any studies indexed after the above searches were done. Other sources including the 2010 and 2011 meeting abstracts of ASCO (American Society of Clinical Oncology), American Urological Association and San Antonio Breast Cancer symposium were also searched. Searches were limited to English language studies only.

Full details of all searches are shown in Appendix 1.

## 5.2 Inclusion and exclusion criteria

### *5.2.1 Types of studies*

The following studies were considered for inclusion:

- Systematic reviews and randomised controlled trials (RCT).

  There was no size restriction on the number of patients in trials, since those with inadequate numbers and hence power, would have been useful when combined in a meta-analysis.

If there were any high quality existing systematic reviews that met the inclusion criteria, we would have considered updating them; however no relevant systematic reviews were identified.

- Observational studies were used, in addition to RCTs, for data on quality of life and safety.

Only studies published in full were included, except for published abstracts that reported additional outcomes or analyses from studies already published in full.

Meeting abstracts were tabulated for use in the discussion to indicate ongoing research (for recent abstracts), or possible sources of publication bias (for older abstracts not subsequently published in full).

### 5.2.2 *Types of participants*

The population considered were adults with confirmed carcinoma of the following:

- breast,
- prostate,
- non-small cell lung cancer (NSCLC), or
- other solid tumours

plus, evidence of at least one bone metastasis.

We considered separately patient groups, based on location or type of primary cancer, where data permitted.

### *5.2.3 Types of interventions*

The intervention is denosumab (trade name Xgeva), manufactured by Amgen, given as a subcutaneous injection at dose of 120 mg every 4 weeks. The approved indication for denosumab is for the prevention of skeletal-related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumours.

We excluded studies (such as pharmacokinetic or drug tolerability studies) where patients were only given a single dose of a drug and where studies compared different routes of administration of the same bisphosphonate. In studies that have arms with more than one dose of a licensed comparator drug, only arms of studies that used the UK licensed doses of the drug were included.

### *5.2.4 Types of comparators*

The relevant comparators are: 1) bisphosphonates, and 2) best supportive care

1) Bisphosphonates

Biphosphonates (BPs) considered as a comparator included:

- sodium clodronate,
- disodium pamidronate,
- ibandronic acid and
- zoledronic acid.

Etidronate was initially considered as an unlicensed (for this purpose) comparator, because of its much lower cost. However, clinical advice suggests infrequent use due to gastrointestinal toxicity.

Currently, zoledronic acid has UK marketing authorisation for the reduction of bone damage in all advanced malignancies involving bone. Disodium pamidronate and sodium clodronate are licensed for breast cancer and multiple myeloma, and ibandronic acid is only licensed for breast cancer. However, we also considered to include trials of these bisphosphonates when used outside their licensed indications.

Clinical experts and NICE guidelines were consulted to determine the place of bisphosphonates in the care pathway. For patient groups in which bisphosphonates are considered the current standard of care, denosumab was compared with bisphosphonates only.

A bisphosphonate class effect was not assumed. As data allowed, all bisphosphonates would be included within a network meta-analysis (NMA).

2) Best supportive care (excluding bisphosphonates)

Best supportive care (BSC) was considered a comparator where bisphosphonates were not recommended. This varied depending on the type of cancer. The relevant NICE Clinical Guidelines are: CG81 for Advanced breast cancer,[45] CG58 for prostate cancer,[46] CG121 for lung cancer[48] and CG75 for metastatic spinal cord compression.[47] All these guidelines recommend radiotherapy and analgesics within best supportive care. Other supportive care for bone metastasis recommended includes surgical fixation in breast cancer and multiple myeloma, strontium-89 in prostate cancer and nerve blocks in lung cancer.

*Breast cancer*

NICE clinical guideline CG81 on breast cancer recommends offering bisphosphonates to patients with newly diagnosed with bone metastases to prevent skeletal-related events and to reduce pain.[45] Therefore BSC was not used as a comparator in patients with advanced breast cancer and bone metastases. The planned network meta-analysis is shown in Figure 1.

*Prostate cancer*

NICE clinical guideline CG58 on prostate cancer recommends that **"**the use of bisphosphonates to prevent or reduce the complications of bone metastases in men with hormone-refractory prostate cancer is not recommended. Bisphosphonates for pain relief may be considered for men with hormone-refractory prostate cancer when other treatments (including analgesics and palliative radiotherapy) have failed."[46] Therefore in prostate cancer denosumab is compared with both bisphosphonates and best supportive care.

*Lung cancer*

No guideline recommendation for the use of BPs exists for bone metastases from lung cancer. NICE Clinical guideline CG121 suggested that there was insufficient evidence to recommend BPs as a first line treatment in the bone metastases from lung cancer.[66] However, the standard treatments such as analgesics, or single fraction radiotherapy, are recommended for the relief of symptoms from bone metastasis.

As the NICE guidelines for prostate and lung cancer recommend best supportive care, before giving a BP, for these patient groups we plan to include BSC as a comparator, where data exists. The planned network meta-analysis for prostate, lung cancer and OST is shown in Figure 2

*Other solid tumours*

In the protocol we stated that if we obtained enough data on other solid tumours for which no relevant NICE guidelines existed, we would seek expert opinion as to the place of BPs in the clinical pathway.

Expert opinion suggested that bisphosphonates, mainly zoledronic acid, were used in other solid tumours. Therefore the network diagram will be as in Figure 2 and denosumab is compared with both bisphosphonates and BSC.

### *5.2.5 Types of outcomes*

These included:

- Time to first on-study skeletal adverse events (SREs) (SRE defined as pathological fracture, requirement for radiation therapy to bone, surgery to bone, or spinal cord compression)
- Time to first-and-subsequent on-study SRE
- SMR
- Incidence of SREs
- Prevention of hypercalcaemia
- Overall survival rate
- Pain
- Health-related quality of life
- Adverse events related to treatment (including hypocalcaemia, osteonecrosis of the jaw (ONJ), renal toxicity, acute phase reactions)

## 5.3 Data extraction strategy

*Selection of studies*

Study selection was made independently by two reviewers (PR, JF) by screening titles, abstracts and full text papers. Discrepancies were resolved by discussion. There was no requirement of a third reviewer.

*Data extraction and management*

Data were extracted from the included studies by one reviewer, using a standardised data extraction form (see Appendix 2), and checked by a second. Discrepancies were resolved by discussion. There was no need of third reviewer. Any study data received from the manufacturer's submission that met the inclusion criteria were extracted and quality assessed in accordance with the procedures outlined in the protocol for the assessment.

## 5.4 Critical appraisal strategy

The quality of the individual studies was assessed by one reviewer, and independently checked for agreement by a second reviewer.

The quality of the RCTs was assessed by using the Cochrane risk of bias tool[67] (see Appendix 3), which includes the following components:

- Adequate sequence generation
- Allocation concealment
- Blinding
- Incomplete outcome data addressed
- Free of selective reporting

Any sponsorship or conflict of interests mentioned was recorded.

## 5.5 Methods of data synthesis

Initially we looked for head-to-head trials of denosumab versus bisphosphonates or best supportive care. Our initial scoping searches indicated that at present there were only three published phase III trials of denosumab which included our relevant population. All three use zoledronic acid as a comparator. The three patient groups included in the three trials are respectively: 1) advanced breast cancer, 2) castration resistant prostate cancer, and 3) patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. Therefore, in order to be able to compare denosumab to bisphosphonates other than zoledronic acid, or to

best supportive care, the search was widened to allow for NMA. This included head-to-head BP trials, placebo controlled BP trials or best supportive care controlled trials.

***Assessment of heterogeneity***

Trials meeting the inclusion criteria were assessed for heterogeneity. The studies were examined for similarity with respect to population, intervention, comparators, outcomes, SRE definition and time frame. If trials were sufficiently homogeneous, a network meta-analysis of denosumab versus bisphosphonates and best supportive care was carried out to pool direct and indirect evidence from randomized trials in a single analysis.

Patient groups were analysed separately based on location or type of primary cancer. When sufficient data were available, subgroup analyses were performed to examine the effect of treatment depending on: the type of SRE, prior history of SREs**,** prior use of bisphosphonate, prior type of best supportive care, different adjuvant therapies, different routes of administration of the bisphosphonates, and the location of the metastases.

An indirect comparison/network meta-analysis was performed as shown in Figures 1 and 2.

**Figure 1 Network meta-analysis for those with bone metastases from breast cancer**

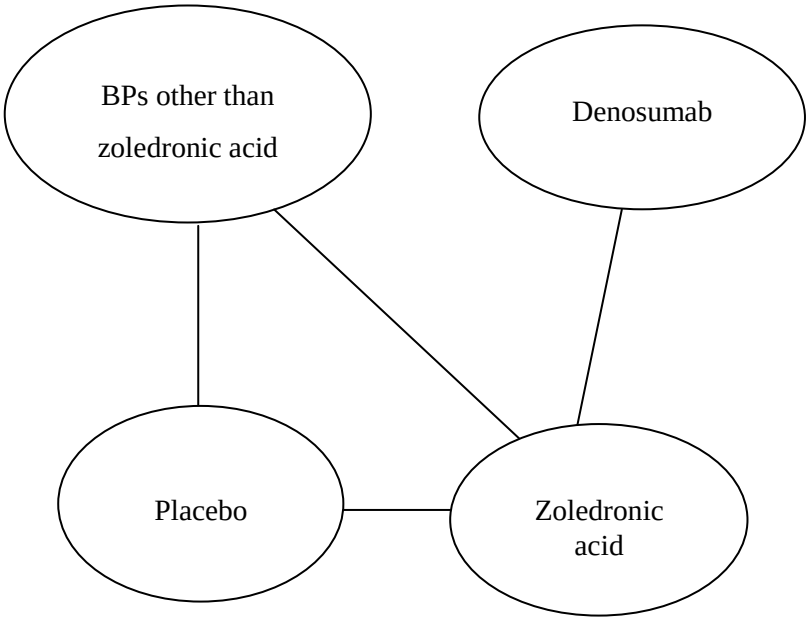
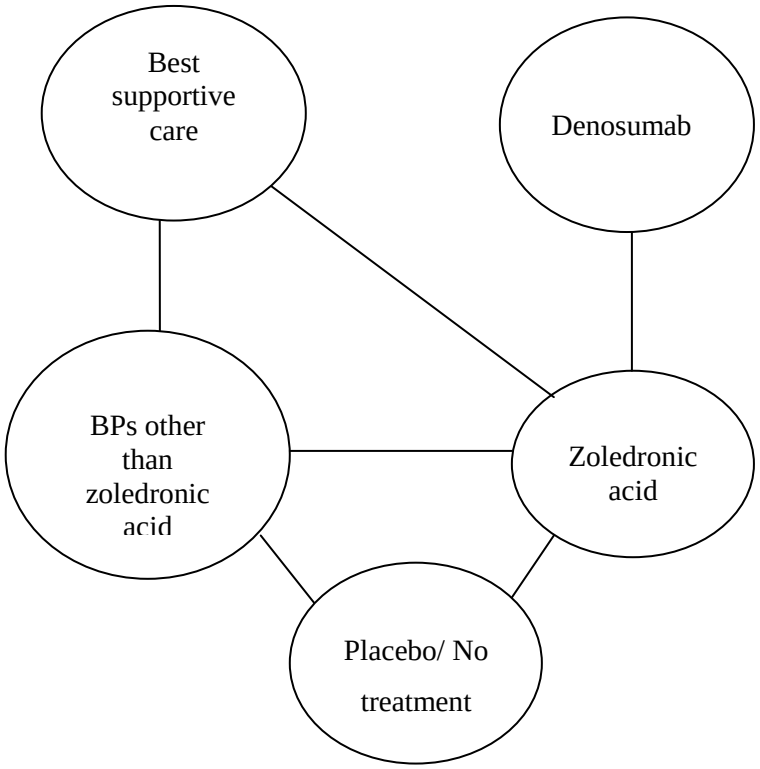


**Figure 2 Network meta-analysis for those with bone metastases from prostate, lung cancer or other solid tumour**




***Statistical technique of NMA***

The network meta-analyses were carried out using methods for mixed treatment comparisons described by Lu and Ades.[68] The Bayesian software package WinBUGS, which employs Markov chain Monte Carlo (MCMC) methods, was used for the analyses.

Network meta-analyses were conducted for all the cancer types included in this appraisal. Outcomes analysed were time to first SRE (hazard ratios), time to first and subsequent SRE (rate ratios from Anderson-Gill[38] multiple event analyses reported in primary studies), skeletal morbidity rate (SMR) ratios (for breast and prostate cancer only) and the proportion of patients with at least one on-study SRE. Proportions of patients with an SRE were also analysed by SRE type for breast and prostate cancer and by SRE history (SRE naive/experienced) for breast cancer.

For time to first SRE, the random effects NMA method proposed by Woods[69] of modelling hazard ratios on the log hazard scale was adopted. One hundred thousand Markov chain Monte simulations were used in the analysis with a thinning parameter of 10 and a burn-in of 100,000. The trial data included in the model comprised log hazard ratios and its standard

error. Pairwise hazard ratios were estimated from the median of the posterior distribution. The analyses included very few trials, so confidence intervals were bootstrapped to address the small amount of data. The same approach was taken for modelling rate ratios in the analysis of time to first and subsequent SREs.

For SMR and proportions of patients with an SRE, random effects models were also used. The data included in the SMR models were mean SMR and standard deviation along with the number of patients. For the proportions with an SRE, the numbers of patients and the numbers with an SRE were used. In the SMR and proportion models, median estimates were taken from 10,000 MCMC simulations after a burn-in of 10,000, with lower and upper 95% confidence limits taken from 2.5% and 97.5% percentiles respectively.

Zoledronic acid was treated as the baseline comparator in each analysis as it is the treatment common to the largest number of trials and is present in multiple included studies for each NMA. Vague priors for baseline risk were specified in the time-to-event analyses, while in the SMR and proportion models, estimates of baseline risk were calculated from data for Zoledronic acid arms pooled across studies.

Some data were missing. Where hazard ratios were not reported or derivable in the primary study, Kaplan-Meier estimates and numbers at risk (if available) were used, applying the methods of Tierney,[70] to estimate the hazard ratio. Mean imputation was used where there was missing data (e.g. standard deviations) in the analysis of skeletal morbidity rates.

***Methods for estimating qualify of life***

Quality of life data for patients who had experienced bone metastases and skeletal related events was obtained from the studies identified from the clinical effectiveness searches, the manufacturer submission, and the denosumab clinical study reports.

A further systematic review of the effects upon quality of life of SREs arising from metastatic bone disease and from myeloma bone disease was undertaken (see chapter 11, section 11.1).

# 6 RESULTS – BREAST CANCER

The clinical effectiveness chapters (6 Breast cancer, 7 Prostate cancer, 8 Non-small cell lung cancer (NSCLC), 9 Other solid tumours (OST) excluding NSCLC and 10 Other solid tumours including NSCLC) follow the same structure. Information is provided on the quantity of research available, followed by the results then a summary of the chapter. For the outcomes of time to first on-study SRE, risk of first-and-subsequent on-study SRE, skeletal morbidity rate and incidence of SREs, information is also reported, where available, for SRE by type, and prior history of SRE. Towards the end of each chapter there is a separate section reporting the results of the network meta-analysis (NMA). Chapters 8 (NSCLC) and 9 (OST excluding NSCLC) are subgroups of one trial. Therefore chapter 10 (OST including NSCLC) has been included to present the outcomes for which the trial was powered and outcomes which are not presented within the aforementioned subgroups.

## 6.1 Quantity of research available – overall review of clinical effectiveness

As a single search strategy was designed to identify all potentially relevant studies for the clinical effectiveness review, information on the overall numbers of studies is given in sections 6.1.1, 6.1.2 and 6.1.3, as well as information specifically relating to breast cancer. The remaining sections from 6.1.4 onwards focus on breast cancer.

### *6.1.1 Number and type of studies included*

*Overall*

A flow diagram outlining the screening process for the overall review of clinical effectiveness is shown in Figure 3.

The searches identified 989 records of which 585 were unique studies (after removing duplicates). Following screening of titles and abstracts, the full text of 352 articles were obtained for further assessment. With the addition of four reports received from the manufacturer, this resulted in 39 studies (74 reports) meeting the inclusion criteria for the review of clinical effectiveness (see Appendix 4). However, of these 39 studies, 31 were not able to contribute data to the Assessment Group's network meta-analysis and none reported denosumab and therefore these studies were not reported further in the results chapters. The reasons why they were not able to contribute data to the network meta-analysis included:

i) Studies did not report uniform definition of skeletal related events, or

ii) Studies did not report standardised skeletal related events rates, or

iii) Studies did not report outcomes separately for different cancer types, or

iv) Studies included patients groups where some patients were not diagnosed with bone metastases.

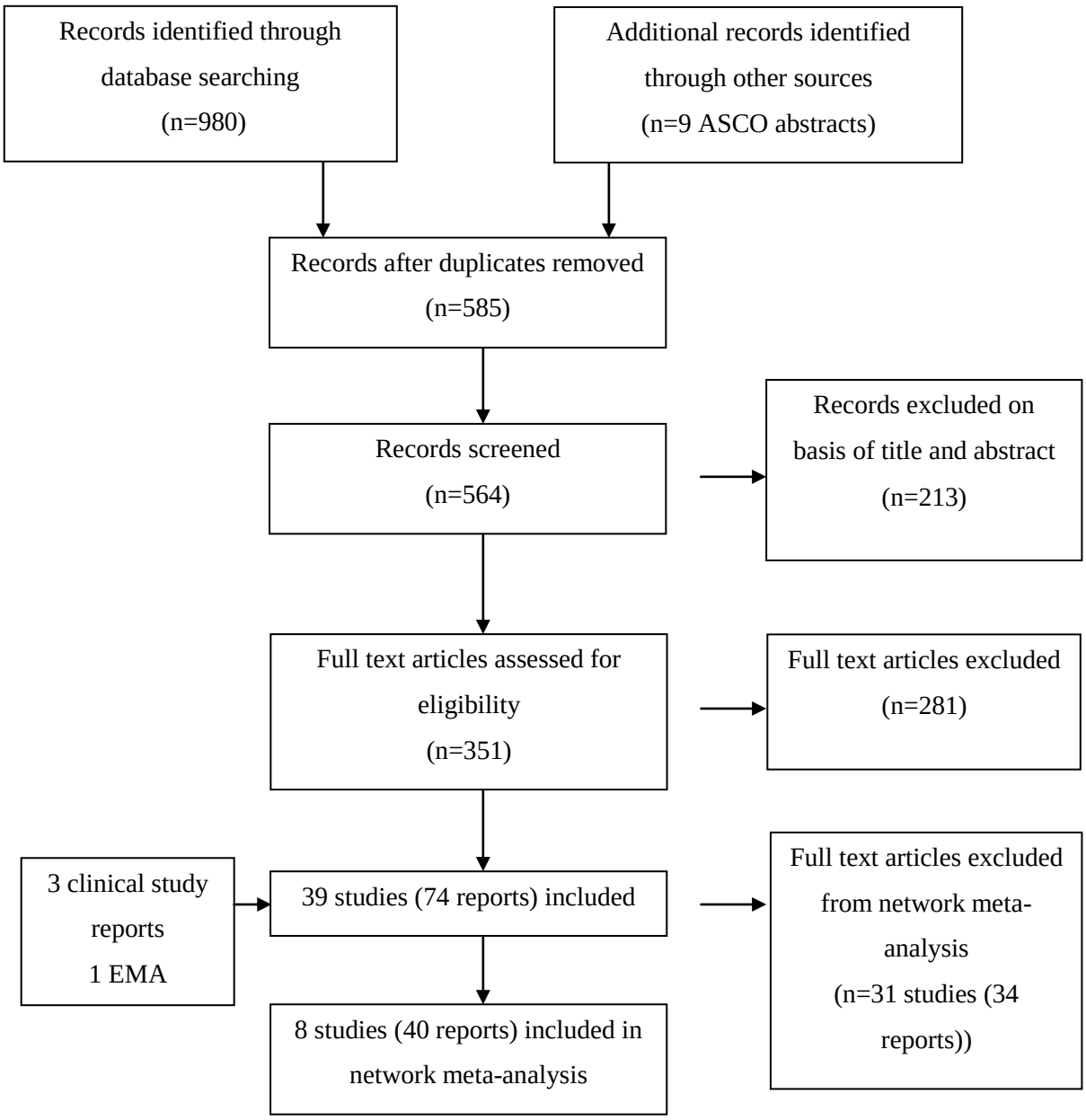
Of these 31 studies, six reported on bone metastases from breast cancer,[71-76] 13 reported on bone metastases from prostate cancer[77-89] and 12 reported on bone metastases from other solid tumours.[90-101]

Of the remaining eight studies that did contribute data to the network meta-analyses, four reported breast cancer[31,102-104] (18 reports[22,31,102-117]), two reported prostate cancer[29,118] (15 reports[19,29,118-130]) and two reported other solid tumours (excluding breast and prostate cancer[30,131] (seven reports[30,131-136]). Therefore across the review of clinical effectiveness eight studies (40 reports) contributed data to the network meta-analyses.

All the included studies were randomised controlled trials (RCTs). No systematic reviews were identified that exactly met our inclusion criteria. The American Society of Clinical Oncology (ASCO) clinical practice guideline update on the role of bone modifying agents in metastatic breast cancer was the most relevant systematic review identified. This review included denosumab, pamidronate and zoledronic acid but did not include ibandronate or clodronate (as they are not licensed for this indication in the USA) and therefore was not considered further.[34]

A search of safety related articles identified twenty eight additional studies.[61,62,137-162]

**Figure 3 Flow diagram of the searches and screening process**




*Breast cancer*

The primary comparator for denosumab was considered to be bisphosphonates (zoledronic acid, disodium pamidronate, ibandronic acid or sodium clodronate) as recommended in the NICE guideline CG81 for all patients with advanced breast cancer and newly diagnosed bone metastases.[45]

One RCT (10 reports,[31,106,107,111-115,117] including Clinical study report 20050136) was identified comparing denosumab with zoledronic acid, with the primary published report considered to be by Stopeck and colleagues.[31] An additional three studies contributed data to the network meta-analysis. One study, by Kohno and colleagues,[102] compared zoledronic acid

with placebo. One study (four reports[22,103,108,116]) compared pamidronate with placebo, with the primary published report considered to be by Lipton and colleagues.[103] One study (three reports[104,109,110]) compared zoledronic acid with pamidronate, with the primary published report considered to be the 2003 paper by Rosen and colleagues.[104]

### *6.1.2 Number and type of studies excluded*

A list of the 281 potentially relevant studies identified by the search strategy for which full text papers were obtained but which subsequently failed to meet the inclusion criteria is given in Appendix 5. These studies were excluded because they failed to meet one or more of the inclusion criteria in terms of the type of study, participants, intervention or outcomes reported. Three trials of denosumab, one in patients with breast cancer,[163] one in patients with prostate cancer[164] and one in patients with other solid tumours[165] were excluded because they used mixtures of bisphosphonates as a comparator and did not report the outcomes separately for each type of bisphosphonate. Table 1 shows the numbers of studies excluded along with the reasons for their exclusion.

**Table 1 Studies excluded from the review after full text screening**

| **Reasons for exclusion** | **Number of studies** |
|---|---|
| Not an RCT<br>• *Reviews*<br>• *Other study design* | 93<br>*69*<br>*24* |
| Comparing doses of radiotherapy | 23 |
| Not a relevant patient group | 26 |
| Dose ranging study | 21 |
| Not a required dose used | 17 |
| No relevant outcomes | 30 |
| Economic study | 10 |
| Adjuvant use of drug | 20 |
| No relevant comparators | 7 |
| No a relevant interventions | 18 |
| Multiple myeloma patient group | 14 |
| Treatment of hypercalcaemia | 2 |
| **Total** | **281** |

### *6.1.3 Characteristics of the included studies*

*Overall*

All 31 studies which were excluded from the network meta-analysis included comparisons of bisphosphonates with placebo or another bisphosphonate and some compared BSC with placebo or another BSC. See Table 2 for a summary of the interventions and comparators included in the trials, and a list of studies included or excluded from the network meta-analysis. Studies meeting the inclusion criteria but not contributing data to the network meta-analysis were not reported on in the chapters on clinical effectiveness as none provided direct evidence on denosumab compared with bisphosphonates, placebo or BSC. However, the results from these studies have been presented in appendices. See Appendix 6 for the characteristics of the participants, description of the interventions/comparators with the reasons for exclusions from the network meta-analysis and Appendix 7 for the results of these studies. Appendix 8 shows the characteristics of the included studies.

**Table 2 Summary of interventions and comparators in the included RCTs**

| Comparison | No of studies | Primary tumour | Intervention | Comparator | Study ID |
|---|---|---|---|---|---|
| **Included in NMA (n=8)** | | | | | |
| ***Denosumab vs zoledronic acid*** | 3 | Breast | Denosumab (sc) | Zoledronic acid (iv) | Stopeck 2010[31] |
| | | Prostate | Denosumab (sc) | Zoledronic acid (iv) | Fizazi 2011[29] |
| | | NSCLC (subgroup) | Denosumab (sc) | Zoledronic acid (iv) | Henry 2011[30] |
| | | OST | Denosumab (sc) | Zoledronic acid (iv) | Henry 2011[30] |
| ***BPs vs placebo/another BP*** | 5 | Breast | Zoledronic acid (iv) | Placebo | Kohno 2005[102] |
| | | Breast | Zoledronic acid (iv) | Pamidronate (iv) | Rosen 2003a[104] |
| | | Breast | Pamidronate (iv) | Placebo | Lipton 2000[103] |
| | | Prostate | Zoledronic acid (iv) | Placebo | Saad 2002[118] |
| | | NSCLC (subgroup) | Zoledronic acid (iv) | Placebo | Rosen 2003b[131] |

| Comparison | No of studies | Primary tumour | Intervention | Comparator | Study ID |
|---|---|---|---|---|---|
| | | OST | Zoledronic acid (iv) | Placebo | Rosen 2003b[131] |
| **Excluded from NMA (n=31)** | | | | | |
| ***BP vs placebo/ another BP*** | 27 | Breast | Ibandronate (oral) | Placebo | Body 2004[72] |
| | | | Ibandronate (iv) | Placebo | Body 2003[71] |
| | | | Ibandronate (iv) | Placebo | Heras 2009[74] |
| | | | Clodronate (oral) | Placebo | Elomaa 1988[73] |
| | | | Clodronate (oral) | Placebo | Paterson 1993[76] |
| | | | Clodronate (oral) | Open | Kristensen 1999[75] |
| | | | Clodronate (oral) | Placebo | Dearnaley 2003[79] |
| | | Prostate | Clodronate (iv) | Placebo | Elomaa 1992[80] |
| | | | Clodronate (iv) | Open | Kylmala 1993[82] |
| | | | Clodronate (iv) | Placebo | Ernst 2003[81] |
| | | | Clodronate (iv+im+oral) | Placebo | Adami 1989[77] |
| | | | Clodronate (iv+oral) | Placebo | Kylmala 1997[83] |
| | | | Clodronate (iv) | Placebo | Strang 1997[89] |
| | | | Pamidronate (iv) | Placebo | Small 2003[87] |
| | | | Etidronate (iv+oral) | Placebo | Smith 1989[88] |
| | | | Clodronate (oral) | Placebo | Arican 1999[90] |
| | | OST | Clodronate (oral) | Placebo | Brown 2007[92] |
| | | | Clodronate (oral) | Placebo | O'Rourke 1995[96] |
| | | | Clodronate (oral) | Placebo | Piga 1998[97] |

| Comparison | No of studies | Primary tumour | Intervention | Comparator | Study ID |
|---|---|---|---|---|---|
| | | | Clodronate (oral) | Placebo | Robertson 1995[98] |
| | | | Clodronate (oral) | Pamidronate (iv) | Jagdev 2001[94] |
| | | | Ibandronate (oral) | Ibandronate (iv) | Mystakidou 2008[95] |
| | | | Ibandronate (iv) | Placebo | Heras 2007[93] |
| | | | Zoledronic acid (iv) | Placebo | Lipton 2003[101] |
| | | | Zoledronic acid (iv) | Pamidronate (iv) | Berenson 2001[91] |
| | | | Zoledronic acid (iv) | Placebo | Zaghloul 2010[99] |
| | | | Zoledronic acid (iv) | Open | Zhao 2011[100] |
| ***BSC vs placebo/ another BSC*** | 4 | Prostate | Strontium chloride (iv) | Placebo | Buchali 1988[78] |
| | | | Strontium chloride (iv) | FEM | Nilsson 2005[84] |
| | | | Strontium chloride (iv) | Placebo | Porter 1993[85] |
| | | | Strontium chloride (iv) | Radiotherapy | Quilty 1994[86] |

**Notes:**

1. BP: bisphosphonates; BSC: best supportive care; FEM: 5-FU, epirubicin and mitomycin C; im: intramuscular; iv: intravenous; NMA: network meta-analysis; OST: other solid tumours; sc: subcutaneous.

*Breast cancer*

Table 3 shows summary information for the four studies that provided direct evidence for denosumab or were included in the network meta-analysis. The study by Kohno and colleagues[102] was undertaken between May 2000 and May 2003 and enrolled adults with at least one osteolytic bone metastasis from breast cancer from 51 centres in Japan. Patients received 4 mg zoledronic acid or placebo every four weeks for 12 months. The primary outcome was the ratio of the SRE rate (defined as the total number of SREs divided by the total years on study) for patients treated with zoledronic acid divided by the SRE rate for the placebo group. Follow-up was 52 weeks. The study was funded by Novartis.

The study by Lipton and colleagues[103] reports results of two similarly conducted RCTs.[22,116] The studies were undertaken between 1990 and 1996 and enrolled women with stage IV breast cancer and at least one predominantly lytic metastatic bone lesion measuring $\geq$ 1 cm from 106 centres in the USA, Canada, Australia and New Zealand. Patients received 90 mg pamidronate every 3-4 weeks or placebo every four weeks for 24 cycles. The primary outcome was the skeletal morbidity rate (SMR), defined as the ratio of the number of skeletal complications experienced by a patient divided by the time on the trial for that patient (expressed as the number of events/year). Follow-up was 24 months. The study was funded by Novartis.

The study by Rosen and colleagues[104] was undertaken between October 1998 and January 2000 and enrolled women with at least 1 bone metastasis (osteolytic, osteoblastic, or mixed) secondary to stage IV breast cancer. The primary analysis of this study included advanced multiple myeloma, but a subgroup of those patients with breast cancer is presented separately.[110] The study was described as multicentre and international. Patients received 4 mg zoledronic acid or 90 mg pamidronate every 3–4 weeks for 24 months. Zoledronic acid was initially infused over five minutes in 50 mL of hydration solution. However, because of concerns over renal safety a protocol amendment in June 1999 changed the infusion time to 15 minutes and increased the volume of the infusion to 100 mL. The primary outcome was the proportion of patients who experienced at least one SRE during the study period. Follow-up was 25 months. The study was funded by Novartis.

The study by Stopeck and colleagues[31] was undertaken between April 2006 and December 2007 and enrolled women with confirmed breast cancer and at least one bone metastasis from 322 centres in Europe, North America, South America, Japan, Australia, India, and South Africa. However only [redacted] of patients were from the UK.(manufacturer submission) Patients with creatinine clearance < 30 mL/min, prior intravenous bisphosphonate treatment, current or prior oral bisphosphonates for the treatment of bone metastases, nonhealed dental/oral surgery, and prior malignancy within three years before random assignment were excluded. Patients received a subcutaneous injection of 120 mg denosumab and an intravenous infusion of placebo or an intravenous infusion of 4 mg zoledronic acid and a subcutaneous injection of placebo every 4 weeks. The study was powered to detect both non-inferiority and superiority with respect to time to first on-study SRE (primary outcome), and risk of first-and-subsequent on-study SREs. Follow-up was around 34 months. The study was funded by Amgen and Daiichi Sankyo.

**Table 3 Characteristics of the studies included in the network meta-analysis**

| | Kohno 2005[102] | | Lipton 2000[103] | | Rosen 2003a[104] | | Stopeck 2010[31] | |
|---|---|---|---|---|---|---|---|---|
| | **ZA** | **Placebo** | **Pamidronate** | **Placebo** | **ZA** | **Pamidronate** | **Denosumab** | **ZA** |
| **Randomised** | 114 | 113 | 367 | 387 | 378 | 388 | 1026 | 1020 |
| **Age** | 54.3 | 53.5 | See notes | | 58 | 56 | 57 | 56 |
| **ECOG status 0-1** | 101 (89%) | 101 (89%) | 265 (72%) | 267 (69%) | (87%) | (81%) | (93%) | (92%) |
| **Time from diagnosis, months:** | | | | | | | | |
| ***Of breast cancer*** | 41.3 | 44.0 | NR | NR | 78±67 | 71±62 | NR | NR |
| ***Of bone metastases*** | 3.9 | 3.9 | See notes | See notes | 17.5±33.85 | 12.6±21.68 | 2.1 | 2.0 |
| **Previous SREs** | 39 (34%) | 47 (42%) | NR | NR | 232 (62%) | 244 (63%) | 378 (37%) | 373 (37%) |

**Notes:**

1. ZA, zoledronic acid; SRE, skeletal related event; NR, not reported.
2. Age. Kohno[102] reported mean. Lipton[103] reported the following breakdown: < 50: Pamidronate (n=92, 25%), Placebo (n=110, 29%); 51-65: Pamidronate (n=154, 42%), Placebo (n=145, 38%); >65: Pamidronate (n=121, 33%), Placebo (n=129, 349%). Rosen[104] and Stopeck[31] reported median.
3. Time from diagnosis. Kohno[102] and Stopeck[31] reported median. Lipton reported the following breakdown: < 2 years: Pamidronate (n=130, 35%), Placebo (n=151, 39%); ≥ 2 years: Pamidronate (n=237, 65%), Placebo (n=233, 61%). Rosen 2003a[104] reported mean ± SD.
4. Kohno 2005[102] only recruited patients from Japan and who had lytic bone lesions.

### *6.1.4 Quality of the included studies*

Table 4 shows the results of the risk of bias assessment for the four studies that were included in the network meta-analysis.

**Table 4 Results of the risk of bias assessment**

| | **Kohno 2005[102]** | **Lipton 2000[103]** | **Rosen 2003a[104]** | **Stopeck 2010a[31]** |
|---|---|---|---|---|
| **Adequate sequence generation** | Yes | Yes | Yes | Unclear |
| **Adequate allocation concealment** | Yes | Yes | Yes | Unclear |
| **Blinding** | Yes | Yes | Yes | Yes |
| **Incomplete outcome data addressed** | No | Unclear | Yes | Yes |
| **Free of selective reporting** | Yes | Unclear | Yes | Yes |

The study by Lipton and colleagues[103] used computer-generated randomisation, while the study by Rosen and colleagues[104] reported an automated system and the study by Kohno and colleagues[102] employed a dynamic balancing method. Although the study by Stopeck and colleagues[31] was described as randomised no further details were given of the sequence generation or allocation concealment. In the study by Lipton and colleagues[103] patients, investigators and other study personnel were blinded, the study by Kohno and colleagues[102] involved blinded radiographic assessment and the studies by Stopeck and colleagues[31] and Rosen and colleagues[104] were described as double blind. The study by Kohno and colleagues[102] did not provide an explanation as to the reasons why around 33% of patients in the zoledronic acid group and 36% in the placebo group did not complete the study. It was unclear in the study by Lipton and colleagues[103] whether the issue of incomplete outcome data had been addressed (reasons for discontinuation stated but number discontinued not given for one trial- Hortobagyi 1996) or whether the study was free of selective reporting of outcomes (the stated primary endpoint and endpoint for power calculation were different for one trial- Theriault 1999).

## 6.2 Assessment of effectiveness

This section reports the clinical effectiveness and safety of denosumab for the treatment of bone metastases from breast cancer compared with BPs or placebo for those comparative studies included in the network meta-analysis. See Appendix 7 for the results for the

following outcomes reported by those studies comparing BPs with placebo that were not included in the network meta-analysis.

### *6.2.1 Time to first on-study SRE*

Table 5 shows the results for time to first on-study SRE as reported in the studies by Lipton and colleagues,[103] Kohno and colleagues,[102] Stopeck and colleagues[31] and Rosen and colleagues.[104]

In the study by Stopeck and colleagues,[31] median time to first on-study SRE was not reached in the denosumab group compared with a median of 26.4 months in the zoledronic acid group during approximately 34 months of follow-up (HR 0.82, 95% CI 0.71 to 0.95, p = < 0.0001). Figure 4 shows the Kaplan-Meier estimates of the time to first on-study SRE. The manufacturer's submission reported that denosumab reduced the risk of a symptomatic SRE by [redacted] and reduced the proportion of patients with symptomatic SREs [redacted] (manufacturer submission). After an extended four months of blinded follow-up, Stopeck and colleagues[31] reported that the median time to first on-study SRE was longer in denosumab group compared with the zoledronic acid group by five months (32.4 versus 27.4 months).

The median time to first on-study SRE was significantly longer in the bisphosphonates group compared with the placebo group in the study by Kohno and colleagues[102] (not reached versus approximately 12 months, p=0.007) and Lipton and colleagues[103] (12.7 (95% CI 9.6 to 17.2) versus 7.0 (95% CI 6.2 to 8.5) months, p<0.001). The median time to first SRE was similar in the bisphosphonates groups as reported in trials by Lipton and colleagues[103] (12.7 months) and Rosen and colleagues[104] (~11.6 to 13.8 months). There was no difference in the time to first SRE including or excluding hypercalcaemia as reported in the trial by Kohno and colleagues.[102]

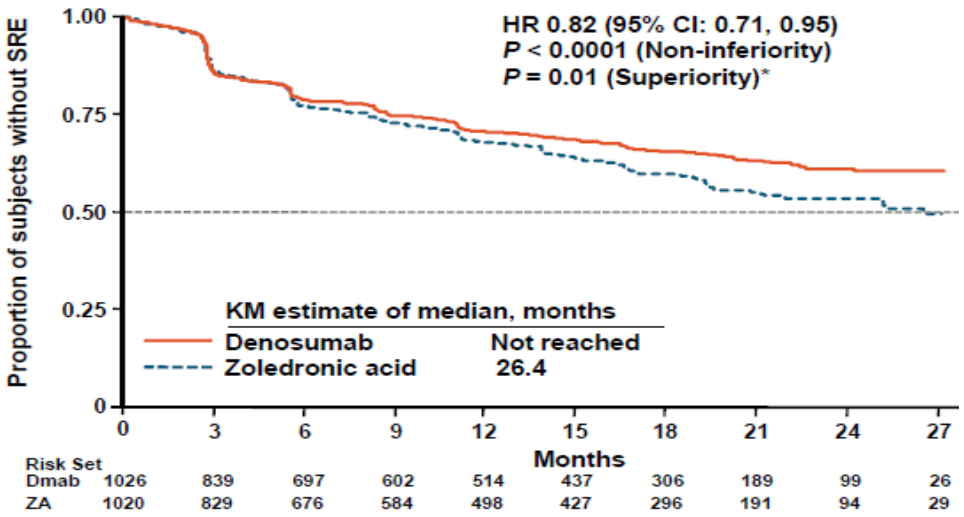
**Table 5 Results for time to first on-study SRE**

| Study ID | Outcomes | Measures | Values | | P value |
|---|---|---|---|---|---|
| | | | **Intervention** | **Comparator** | |
| **Stopeck 2010[31]** | | | ***Denosumab (n=1026)*** | ***ZA (n=1020)*** | |
| | †Time to first SRE, (~34 months study duration) | Median months | Not reached | 26.4 | NA |
| | Time to first SRE, (from 4 months extended treatment phase) | Median months | 32.4 | 27.4 | NA |
| | Delay to first on-study skeletal-related events | Hazard ratio (95%CI) | 0.82 (0.71 to 0.95) | | p<0.01 (superiority analysis) |
| **Kohno 2005[102]†** | | | ***ZA (n=114)*** | ***Placebo (n=113)*** | |
| | Time to first SRE (excluding HCM) | Median days | Not reached | 364 (~12.1 months) | 0.007 |
| | Time to first SRE (including HCM) | Median days | Not reached | 360 (~12 months) | 0.004 |
| **Lipton 2000[103]** | | | ***Pamidronate (n=367)*** | ***Placebo (n=387)*** | |
| | Time to any first SRE | Median months (95% CI) | 12.7 (9.6 to 17.2) | 7.0 (6.2 to 8.5) | <0.001 |
| | Time to first pathological fracture | Median months | 25.2 | 12.8 | 0.003 |
| | Time before requiring bone radiation | Median months | Not reached | 16.0 | <0.001 |
| **Rosen 2003a[104]** | | | ***ZA (n=378)*** | ***Pamidronate (n=388)*** | |
| | Time to first SRE (chemotherapy treated) | Median days | 349 (~11.6 months) | 366 (~12.2 months) | 0.826 |
| | Time to first SRE (hormonal therapy treated) | Median days | 370 (~12.3 months) | 415 (~13.8 months) | 0.047 |
| | Time to first SRE (lytic) | Median days | 310 (~10.3 months) | 174 (~5.8 months) | 0.013 |
| | Time to first SRE (non-lytic) | Median days | NR | NR | NR |

Note: †Cox regression(Wald test of the regression coefficient) stratified by prior fracture; NR: not reported; NS: not significant; 1 month= 30 days

NA: not applicable

**Figure 4 Kaplan-Meier estimates of time to first on-study SRE**




Source: manufacturer submission.

*SRE by type*

In the denosumab RCT Stopeck and colleagues[31] did not report SRE by type. The manufacturer's submission reported that denosumab reduced the risk for time to radiation in bone by [redacted] compared to zoledronic acid. Table 6 shows the distribution of first on-study SRE by type of SRE in the denosumab study. The distribution of type of SRE was similar across the treatment groups, with radiation to bone and pathological fracture being the most commonly occurring.

**Table 6 Patients with first on-study SRE by type**

| | **Denosumab (n=1026 randomised)** | **Zoledronic acid (n=1020 randomised)** |
|---|---|---|
| | **Number of events (%)** | **Number of events (%)** |
| **Overall** | 315 (100%) | 372 (100%) |
| **Radiation to bone** | [redacted] | [redacted] |
| **Pathological fracture** | [redacted] | [redacted] |
| **Spinal cord compression** | [redacted] | [redacted] |
| **Surgery to bone** | [redacted] | [redacted] |

Source: manufacturer submission.

In the study by Lipton and colleagues,[103] the median time to first pathological fracture was significantly longer in the pamidronate group compared with the placebo group (by almost 12 months). The time before requiring bone radiation was not reached in the pamidronate group compared with a median of 16 months in the placebo group ($p<0.001$).[103]

*Prior history of SRE*

The manufacturer's submission reported time to first on-study SRE by prior history of SRE for the denosumab study 103 (Table 7). This showed that for those without a prior SRE [redacted]. Covariate analysis showed that patients with a prior SRE history had an increased risk of [redacted] compared with those without an SRE history.

**Table 7 Time to first on-study SRE by prior history of SRE**

| | | Denosumab | Zoledronic acid |
|---|---|---|---|
| **Overall** | **Number** | 1026 | 1020 |
| | **HR (95% CI)** | 0.82 (0.71, 0.95) | |
| | **p-value** | 0.0101 | |
| **No prior SRE** | **Number** | 648 | 647 |
| | **HR (95% CI)** | [redacted] | |
| | **p-value** | [redacted] | |
| **Prior SRE** | **Number** | 378 | 373 |
| | **HR (95% CI)** | [redacted] | |
| | **p-value** | [redacted] | |
| **Covariate effect** | **Pt estimate (95% CI)** | [redacted] | |
| | **P value** | [redacted] | |

Source: manufacturer submission.

**Notes:**

1. Hazard ratio (HR) based on the Cox proportional hazards model with treatment groups as independent variables and stratified by the randomisation stratification factors.

The study by Rosen and colleagues,[104] comparing zoledronic acid with pamidronate, reported time to first on-study SRE by lytic and non-lytic sub group. There was no significant

difference between the non-lytic treatment groups. For those lytic cases, the time to first SRE was much longer in the zoledronic acid (~10.3 months) group compared with the pamidronate group (~5.8 months).

### *6.2.2 Risk of first-and subsequent on-study SRE*

Table 8 shows the results for risk of first-and-subsequent on-study SRE.

Stopeck and colleagues[31] reported a risk reduction of 23% (RR 0.77 (95% CI 0.66 to 0.89), p=0.001) for the denosumab group compared with the zoledronic acid group over 34 months, with the risk remaining similar when the duration of treatment was extended by another four months (RR 0.78 (95% CI 0.68 to 0.90), p=0.002). Figure 5 shows the cumulative mean number of SREs (multiple event analysis).

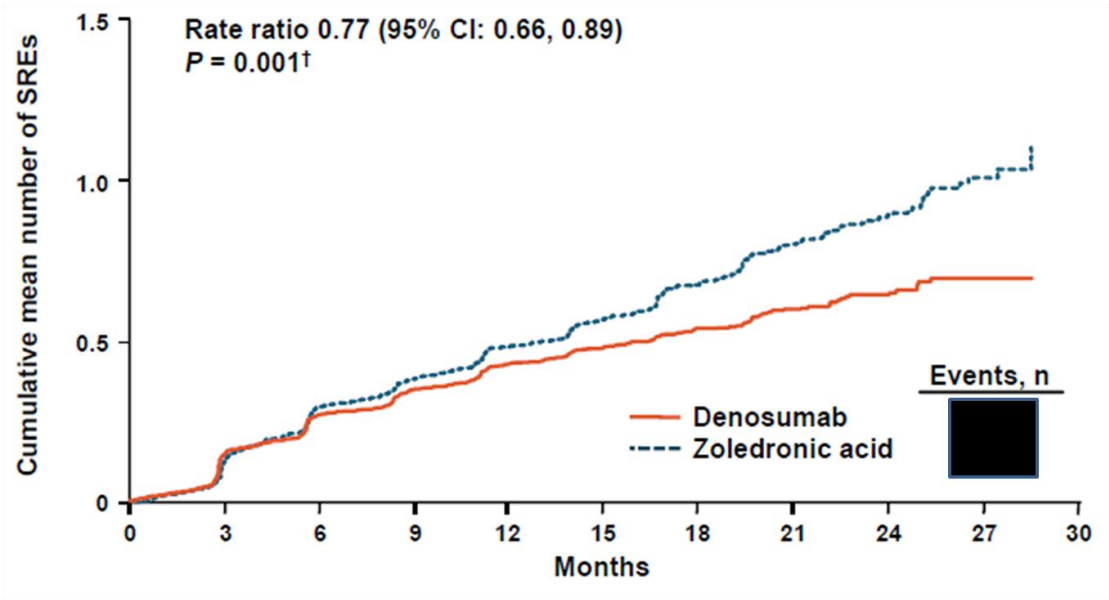
Kohno and colleagues[102] and Rosen and colleagues[104] reported the risk for developing multiple SREs for zoledronic acid compared with placebo and pamidronate respectively. In both studies, zoledronic acid significantly reduced the risk of developing multiple SREs when hypercalcaemia of malignancy was included in the SRE analysis (44% reduction compared with placebo[102] and approximately 20% reduction compared with pamidronate.[104] Similar results were reported when hypercalcaemia of malignancy was excluded from the SRE analysis (the risk of developing multiple SREs was 41% lower in the zoledronic group compared with the placebo group and 20% lower compared with the pamidronate group).

**Table 8 Results for risk of first-and-subsequent on-study SRE**

| Study ID | Treatment duration | Outcomes | Measures | Values, variance | | P value |
|---|---|---|---|---|---|---|
| | | | | **Intervention** | **Comparator** | |
| **Stopeck 2010[31]** | ~34 months | | | ***Denosumab(n=1026)*** | ***ZA(n=1020)*** | |
| | | Risk of developing multiple SREs | Rate ratio (95%CI) | 0.77 (0.66 to 0.89) | | 0.001 |
| | from 4 months extended treatment phase | Risk of first and subsequent on study SRE | Rate ratio (95% CI) | 0.78 (0.68, 0.90) | | 0.002 |
| **Kohno 2005[102]** | | | | ***ZA(n=114)*** | ***Placebo(n=113)*** | |
| | 12 months | Risk for developing SREs (multiple event analysis) Excluding HCM | Risk ratio (95%CI) | 0.59 (0.375 to 0.914) | | .019† |
| | | Risk for developing SREs (multiple event analysis) Including HCM | Risk ratio (95%CI) | 0.56 (0.363 to 0.867) | | .009† |
| **Rosen 2003a[104]** | | | | ***ZA(n=378)*** | ***Pamidronate (n=388)*** | |
| | 25 months | Risk of developing any SRE(multiple event analysis) Including HCM | Risk ratio (95%CI) | 0.799(0.657 to 0.972) | | P=0.025 |
| | 25 months | Risk of developing a SRE Including HCM – hormone therapy treated | Risk ratio (95%CI) | 0.693(0.527 to 0.911) | | P=0.009 |
| | 13 months | Risk for multiple skeletal events (total) Excluding HCM | Hazard ratio (95%CI) | 0.801(Not reported) | | P=0.037 |
| | 13 months | Risk for multiple skeletal events (lytic) excluding HCM | Hazard ratio (95%CI) | 0.704 (Not reported) | | P=0.010 |
| | 13 months | Risk for multiple skeletal events (non-lytic) excluding HCM | Not reported | Not reported | | P=0.760 |

†Wald test of the regression coefficient) stratified by prior fracture

**Figure 5 Cumulative mean number of SREs (multiple event analysis)**




Source: Manufacturer submission

*SRE by type*

None of the studies reported risk of first-and-subsequent SREs by individual SRE type.

The manufacturer's submission reported the distribution of first-and-subsequent on-study SRE by type of SRE in the denosumab RCT (study 136) (Table 9). As for first on-study SRE by type, the distribution of type of SRE was similar across the treatment groups, with radiation to bone and pathological fracture again the most commonly occurring.

**Table 9 Distribution of first-and-subsequent SRE by type – with 21 day window**

| | **Denosumab (n=1026 randomised)** | **Zoledronic acid (n=1020 randomised)** |
|---|---|---|
| | **Number of events (%)** | **Number of events (%)** |
| **Total confirmed events** | [redacted] | [redacted] |
| **Radiation to bone** | [redacted] | [redacted] |
| **Pathological fracture** | [redacted] | [redacted] |
| **Spinal cord compression** | [redacted] | [redacted] |
| **Surgery to bone** | [redacted] | [redacted] |

Source: manufacturer submission.

*Prior history of SRE*

The manufacturer's submission reported risk of first-and-subsequent on-study SRE by prior history of SRE for study 136 (Table 10). [redacted] Covariate analysis as presented in the manufacturer's table showed that patients with a prior SRE history had an increased risk of [redacted] compared with those without an SRE history.

**Table 10 Risk of first-and-subsequent on-study SRE by prior history of SRE**

| | | Denosumab | Zoledronic acid |
|---|---|---|---|
| **Overall** | **Number** | 1026 | 1020 |
| | **RR (95% CI)** | [redacted] | |
| | **p-value** | [redacted] | |
| **No prior SRE** | **Number** | 648 | 647 |
| | **RR (95% CI)** | [redacted] | |
| | **p-value** | [redacted] | |
| **Prior SRE** | **Number** | 378 | 373 |
| | **RR (95% CI)** | [redacted] | |
| | **p-value** | [redacted] | |
| **Covariate effect** | **Pt estimate (95% CI)** | [redacted] | |
| | **p value** | [redacted] | |

Source: manufacturer submission.

**Notes:**

1. Rate ratio (RR) based on the Anderson-Gill model stratified by the randomised stratification factors.

Rosen and colleagues[104] reported a 30% reduction in the risk of multiple SREs (excluding hypercalcaemia of malignancy) for zoledronic acid compared with pamidronate in the sub group of patients with lytic lesions (HR 0.704, p=0.010), while the risk reduction was non-significant in those with non-lytic lesions (p=0.760).

### *6.2.3 Skeletal morbidity rate*

Table 11 shows the results for skeletal morbidity rate. The skeletal morbidity rate (SMR) is defined as the ratio of the number of SREs per patient divided by the patient's time at risk. The manufacturer's submission stated that for the SMR calculations a 21-day event window was used for counting on-study SREs, so that any event occurring within 21 days of a previous event was not counted as a separate on-study SRE.

Stopeck and colleagues[31] reported that the mean SMR (ratio of the number of SREs per patient divided by the patient's time at risk) was significantly lower in the denosumab group (0.45 events per patient per year) compared with the zoledronic acid group (0.58 events per patient per year) ($p = 0.004$). The studies by Kohno and colleagues[102] and Lipton and colleagues,[103] comparing bisphosphonates with placebo reported that SRE events occurred less frequently in the bisphosphonates group (0.63 to 2.4 events per year) than in the placebo group (1.1 to 3.7 events per year). In the study by Rosen and colleagues[104] the SMR rate was lower for zoledronic acid compared with pamidronate (0.9 events per year versus 1.49 events per year), although the difference was not statistically significant ($p=0.125$). In the study by Kohno and colleagues[102] the rate of SREs was reduced by 39% (0.61, $p=0.027$) in the zoledronic acid group compared with the placebo group when adjusted for whether or not patients had experienced prior pathological fracture before study entry. A similar SMR was reported when hypercalcaemia of malignancy was included or excluded from the analysis in the studies by Lipton and colleagues[103] and Rosen and colleagues.[104]

*SRE by type*

The manufacturer's submission did not report SMR by type of SRE.

The study by Lipton and colleagues[103] comparing pamidronate with placebo reported SMR for different types of SREs including radiation to bone, radiation to bone for pain relief, pathologic fracture, surgery to bone, spinal cord compression and hypercalcaemia. A statistically significant difference was reported between pamidronate and placebo for all types of SRE other than spinal cord compression. Among all the SREs, the highest rate (events per year) was reported for pathological fracture (1.6 versus 2.2) and the lowest rate was reported for spinal cord compression (0.07 versus 1.75).

*Prior history of SRE*

The manufacturer's submission did not report SMR by prior history of SRE.

In the study by Kohno and colleagues[102] the SRE rate reduction for zoledronic acid was more than 30% higher in patients without a prior fracture (unadjusted SRE rate ratio 0.43) than in patients with a prior fracture (unadjusted SRE rate ratio 0.81).

In the sub group analysis of patients with lytic lesions, Rosen and colleagues[104] reported SRE rates in the zoledronic acid arm (1.16 events per year) almost half of those in the pamidronate arm (2.36 events per year), p=0.008. In those with non-lytic lesions, the difference between the treatment groups for SRE rate was reported to be non-significant (0.81 versus 0.97, p=0.904).

**Table 11 Skeletal morbidity rate**

| Study ID | Treatment duration | Outcomes | Measures | Values, variance | | Difference between groups | P value |
|---|---|---|---|---|---|---|---|
| | | | | **Intervention** | **Comparator** | | |
| **Stopeck 2010[31]** | ~34 months | | | ***Denosumab(n=1026)*** | ***ZA (n=1020)*** | | |
| | | SMR (defined as the ratio of the number of SREs per patient/the patient's time at risk) | Mean events per patient per year | 0.45 | 0.58 | Denosumab reduced risk by 22% | 0.004 |
| | | | | ***ZA (n=114)*** | ***Placebo (n=113)*** | | |
| **Kohno 2005[102]** | 12 months | SRE rate (defined as the total number of SREs divided by the total years on study)<br>All patient | No of events per patient years | 0.63 | 1.1 | SRE rate ratio= 0.57 (unadjusted) | 0.016 |
| | | SRE rate<br>Patients with prior fracture | No of events per patient years | 1.55 | 1.91 | SRE rate ratio= 0.81 (Unadjusted)<br>0.61 (Adjusted)* | 0.027 |
| | | SRE rate<br>Patients without prior fracture | No of events per patient years | 0.33 | 0.78 | SRE rate ratio= 0.43 (unadjusted) | |
| | | | | ***Pamidronate (n=367)*** | ***Placebo (n=387)*** | | |
| **Lipton 2000[103]** | 24 months | SMR (any skeletal complication excluding HCM) | No of events per year (mean, SD) | 2.4 (5.5) | 3.7 (5.5) | Not reported | <0.001 |
| | | SMR (any skeletal complication including HCM) | No of events per year (mean, SD) | 2.5 (5.6) | 4.0 (6.1) | Not reported | <0.001 |
| | | Radiation to bone | No of events per year (mean, SD) | 0.7 (1.9) | 1.2 (2.4) | Not reported | <0.001 |
| | | Radiation to bone for pain relief | | 0.5 (1.6) | 1.0 (2.2) | Not reported | <0.001 |
| | | Pathologic fracture | | 1.6 (4.1) | 2.2 (4.5) | Not reported | 0.002 |
| | | Surgery to bone | | 0.10 (0.58) | 0.15 (0.53) | Not reported | 0.009 |

| Study ID | Treatment duration | Outcomes | Measures | Values, variance | | Difference between groups | P value |
|---|---|---|---|---|---|---|---|
| | | | | Intervention | Comparator | | |
| | | Spinal cord compression | | 0.04 (0.30) | 0.07 (0.60) | Not reported | 0.772 |
| | | Hypercalcaemia | | 0.07 (0.36) | 0.37 (1.75) | Not reported | <0.001 |
| **Rosen 2003a[104]** | | | | ***ZA (n= 378)*** | ***Pamidronate (n= 388)*** | | |
| | 25 months | SMR excluding HCM | Events per year | 0.9 | 1.49 | Not reported | 0.125 |
| | 25 months | SMR including HCM | Events per year | 0.91 | 1.57 | Not reported | 0.102 |
| | 25 months | SMR (hormonal treated) | Events per year | 0.83 | 1.37 | Not reported | 0.39 |
| | 13 months | SMR excluding HCM | Events per year, mean (SD) | 0.98 (2.04) | 1.55 (SD 5.03) | Not reported | 0.073 |
| | 13 months | SMR lytic | Events per year, mean (SD) | 1.16 (2.32) | 2.36 (7.16) | Not reported | 0.008 |
| | 13 months | SMR non-lytic | Events per year, mean (SD) | 0.81 (1.69) | 0.97 (2.47) | Not reported | 0.904 |
| | 13 months | SMR hormonal therapy treated | Events/year | 0.33 | 0.58 | Not reported | 0.015 |

SRE rate ratio: SRE rate for patients treated with ZA divided by the SRE rate for the placebo
*adjusted based on whether patients had or had not experienced a pathologic fracture before study entry)

### *6.2.4 Incidence of SREs*

Table 12 shows the results for the crude incidence of SREs.

Stopeck and colleagues[31] reported that at approximately 34 months of treatment, 30.7% of those receiving denosumab compared with 36.5% receiving zoledronic acid experienced any on-study SRE. The manufacturer's submission reported an annualised SRE rate based on the number of SREs observed in each treatment arm divided by the number of patient-years for each treatment arm and reported this outcome both with and without a 21-day event window.

Table 13 shows the annualised SRE rate both with and without the 21-day window for study 136. The manufacturer's submission reported that the primary analysis of annualised SRE rates was based on all SREs reported in each arm of the study (calculated without a 21-day window). Subsequently, a post-hoc analysis of the annualised SRE rate applying the trial-defined 21-day window for SREs was conducted. Both analyses show that the annualised SRE rate was lower in patients receiving denosumab compared with those receiving zoledronic acid.

A statistically significant difference in favour of bisphosphonates compared with placebo for patients experiencing an on-study SRE was reported in the studies by Kohno and colleagues[102] and Lipton and colleagues.[103] The proportion of patients experiencing at least one on-study SRE at one year was significantly lower by 20% in the zoledronic acid group compared with the placebo group (29.8% versus 49.6%) in the study by Kohno and colleagues.[102] In the study by Lipton and colleagues,[103] at two years, the pamidronate group experienced a lower rate of SREs compared with the placebo group (51% versus 64%).[103] Rosen and colleagues,[104] comparing zoledronic acid with pamidronate, reported a non-significant difference between the groups for the crude incidence of SREs at 13 or 25 months. Rosen and colleagues further reported non-significant difference in the crude incidence of SREs between zoledronic acid and pamidronate for those with lytic lesion. For those with non-lytic lesion similar crude incidence was reported between the groups.

**Table 12 Crude incidence of on study SREs**

| Study ID | Outcomes | Measures | Values, variance | | P value |
|---|---|---|---|---|---|
| | | | **Intervention** | **Comparator** | |
| | | | ***Denosumab (n=1026)*** | ***ZA (n=1020)*** | |
| **Stopeck 2010[31]** | Proportion of patients who experienced any on study SRE | At 34 months | 30.7% | 36.5% | NR |
| | | | ***ZA (n=114)*** | ***Placebo (n=113)*** | |
| **Kohno 2005[102]** | Proportion of patients with at least one SRE (excluding HCM) | At 1 year | 29.8% | 49.6% | 0.003 |
| | Proportion of patients with at least one SRE (including HCM) | | 30.7% | 52.2% | 0.001 |
| | Proportion with fractures | At 1 year | 25.4% | 38.9% | NR |
| | Proportion with radiation to bone | At 1 year | 8.8% | 17.7% | NR |
| | Proportion with surgery to bone | At 1 year | 0.0% | 0.9% | NR |
| | Proportion with spinal cord compression | At 1 year | 3.5% | 11.5% | NR |
| | Proportion with hypercalcaemia | At 1 year | 2.6% | 8.8% | NR |
| | | | ***Pamidronate (n=367)*** | ***Placebo (n=387)*** | |
| **Lipton 2000[103]** | Proportion with any SRE (excluding HCM) | At 2 years | 51% | 64% | <0.001 |
| | Proportion with any SRE (including HCM) | At 2 years | 53% | 68% | <0.001 |
| | Proportion with radiation to bone | At 2 years | 29% | 43% | <0.001 |
| | Proportion with radiation to bone for pain relief | At 2 years | 25% | 37% | <0.001 |
| | Proportion with pathologic fracture | At 2 years | 40% | 52% | 0.002 |
| | Proportion with surgery to bone | At 2 years | 6% | 11% | 0.008 |
| | Proportion with spinal cord compression | At 2 years | 3% | 3% | 0.762 |
| | Proportion with hypercalcaemia | At 2 years | 6% | 13% | 0.001 |
| | | | ***ZA (n=378)*** | ***Pamidronate (n=388)*** | |

| | | | | | |
|---|---|---|---|---|---|
| **Rosen 2003a[104]** | Proportion with any SRE (excluding HCM) | At 25 months | 46% | 49% | NR |
| | | At 13 months | 43% | 45% | NS |
| | Proportion with any SRE- lytic subgroup | At 13 months | 48% | 58% | 0.58 |
| | Proportion with any SRE- non- lytic subgroup | At 13 months | 38% | 36% | NR |

**Notes:**

1. HCM, hypercalcaemia; SRE, skeletal-related event; ZA, zoledronic acid.

**Table 13 Annualised SRE rate in study 136**

| | Denosumab (n=1026) | Zoledronic acid (n=1020) |
|---|---|---|
| **Annualised SRE rate per patient** | | |
| Subject years | [redacted] | [redacted] |
| **Without 21-day window** | | |
| Number of events | [redacted] | [redacted] |
| Annualised rate | [redacted] | [redacted] |
| **With 21-day window** | | |
| Number of events | [redacted] | [redacted] |
| Annualised rate | [redacted] | [redacted] |

Source: manufacturer submission.

*SRE by type*

The manufacturer's submission did not report this outcome.

The studies by Kohno and colleagues[102] and Lipton and colleagues[103] reported the proportions of patients experiencing types of SRE at one year and two years respectively. For each type of SRE reported (other than for spinal cord compression in the study by Lipton and colleagues[103]), the bisphosphonate group experienced lower rates compared with placebo. In the study by Lipton and colleagues,[103] the difference between the treatment groups for each type of SRE was statistically significant other than for spinal cord compression. In both studies the most frequently occurring type of SRE was fractures (25.4% versus 39.8% at one year in the study by Kohno and colleagues[102] and 40% versus 52% at two years in the study by Lipton and colleagues[103]), followed by radiation to the bone.

In a subgroup analysis comparing patients with lytic and non-lytic lesions, Rosen and colleagues[104] reported a non-significant difference for the proportion experiencing an SRE between zoledronic acid and pamidronate in each subgroup at 13 months.

*Prior history of SRE*

None of the studies reported incidence of SRE by prior history of SRE.

### *6.2.5 Prevention of hypercalcaemia*

In study 136, [redacted].(clinical study report 136)

Kohno and colleagues[102] reported that 2.6% (3/114) of the zoledronic acid group and 8.8% (10/113) of the placebo group experienced hypercalcaemia.

### *6.2.6 Overall survival*

A non-significant difference in overall survival was reported for denosumab compared with zoledronic acid in the study by Stopeck and colleagues[31] (HR 0.95 (0.81 to 1.11), p=0.49). The manufacturer's submission reported this as [redacted] months for denosumab versus [redacted] for zoledronic acid.(manufacturer submission) In the study by Lipton and colleagues[103] overall median survival was slightly longer in the pamidronate group (19.8 months) compared with the placebo group (17.8 months) although the difference was not statistically significant (p=0.976). In a subgroup analysis of women <50 years Lipton and colleagues[103] reported a significantly longer median overall survival in the pamidronate group compared with the placebo group (24.6 versus 15.7 months, p=0.009).

*Prior history of SRE*

None of the studies reported overall survival by prior history of SRE.

### *6.2.7 Pain*

Stopeck and colleagues[31] reported the proportion of patients with no/mild pain at baseline (n = 1042) developing moderate/severe pain at study visits for up to 73 weeks. The severity of pain and interference with daily functioning were assessed using the Brief Pain Inventory-Short Form (BPI-SF) instrument, completed by patients at baseline, day 8 and before each monthly visit through to the end of the study. In each study visit week, the proportion of patients with no/mild pain at baseline, reporting moderate/severe pain was lower in the denosumab group (range 14.8% at 73 weeks to 19.9% at 25 weeks) compared with the zoledronic acid group (range 22.1% at 13 weeks to 27.4% at 37 weeks). The median time to developing moderate/severe pain in patients with no/mild pain at baseline was reported to be significantly longer in the denosumab group compared with the zoledronic acid group (295 versus 176 days; HR 0.78, 95% CI: 0.67 to 0.92; p=0.0024).

The median time to worsening pain (≥ 2 point increase from baseline in BPI-SF worst pain score) non-significantly favoured denosumab compared with zoledronic acid ([redacted] versus [redacted] months, [redacted]) and was similar between groups for time to pain improvement (median 82 days versus 85 days; HR 1.02, 95%CI: 0.91 to 1.15; p=0.7245).

[redacted].(manufacturer submission)

There was no statistical difference at study end point in the use of strong analgesics in breast cancer. [redacted](manufacturer submission)

[redacted](CSR 136)

Lipton and colleagues[103] reported, for pamidronate compared with placebo, mean change in pain scores and analgesic scores from baseline to 24 months. Bone pain was evaluated using a scoring system that quantified both the severity and frequency of bone pain.[103] The bone pain score was determined by multiplying the bone pain severity score by the bone pain frequency score. The mean pain score decreased significantly in the pamidronate group (-0.07, SD 3.07) compared with the placebo group (1.14, SD 3.42) over the 24 months (p=0.015). Similarly, the mean analgesic score decreased significantly in the pamidronate group (-0.06, SD 3.28) compared with the placebo group (1.84, SD 3.73). At the last visit an increased mean pain score and analgesic score was reported in both groups but was significantly lower in the pamidronate group compared with the placebo group (p<0.001).

### *6.2.8 Health related quality of life*

*FACT*

The FACT-B questionnaire consists of the FACT-G questionnaire plus additional questions specific to breast cancer. For each component of the FACT-B (FACT-G total score, FACT-B total score, physical well-being domain, functional well-being domain, and Trial outcome index (TOI, a composite of the functional well-being domain, physical well-being domain, and the prostate cancer subscale)), a higher score indicates better HRQOL.

Stopeck and colleagues[31] reported quality of life using the FACT-G questionnaire completed by patients at baseline, day 8, and before each monthly visit through to the end of the study (73 weeks). At 73 weeks 30% of patients had discontinued the study. [redacted](CSR 136)

Patients were divided into two sub-groups at baseline, no/mild pain or moderate/severe pain based on BPI. For those with no/mild pain at baseline, an average of 4.1% more patients (range -0.6% to 9.3%) treated with denosumab had a ≥5 point increase in the FACT-G score and an average of 2.4% fewer patients (range -4.4% to 6.3%) had a ≥5 point decrease in the FACT-G score at 18 months compared with those patients treated with zoledronic acid. For those with moderate/severe pain at baseline, a similar proportion of patients treated with denosumab had either a ≥5 point increase (average 3% more; range -1.7% to 7.9%) or decrease (average 3.5% fewer; range -1.1% to11.5%) in the FACT-G score at 18 months compared with those treated with zoledronic acid.[107] An average of 3.2% (range 1% to 7%) more patients in the denosumab group experienced a clinically meaningful improvement in quality of life (≥5 point increase in FACT-G total score) from week 5 through to week 73.[106]

*EQ-5D*

For both components of EQ-5D (the health index and the visual analogue scale (VAS)), a higher score indicates a more preferred health status. [redacted] (CSR 136)

[redacted].(CSR 136)

Lipton and colleagues,[103] comparing pamidronate with placebo, reported mean change in the quality of life scores from baseline to 24 months and to the last visit. Quality of life was evaluated using the Spitzer quality of life index. From baseline to the last visit quality of life worsened in both the pamidronate group (-1.80, SD 2.81) and the placebo group (-2.13, SD 2.63) (p=0.088).

### *6.2.9 Adverse events related to treatment*

*Hypocalcaemia*

The manufacturer's submission reported that hypocalcaemia events were mainly non-serious and transient and either resolved spontaneously or with calcium supplementation.(manufacturer submission) More hypocalcaemia adverse events occurred in the denosumab group than in the zoledronic acid group (5.5% (56/1020) versus 3.4% (34/1013) respectively.

Kohno and colleagues[102] reported that 39% of the zoledronic acid group and 7% of the placebo group experienced grade 1 hypocalcaemia. There were no grade 2 or 3 hypocalcaemia events in the

zoledronic acid group, while one patient in each group experienced grade 4 hypocalcaemia.[102] Lipton and colleagues,[103] comparing pamidronate with placebo, reported that one patient (1/367) discontinued pamidronate after a symptomatic hypocalcaemia episode. Rosen and colleagues[104] did not report this outcome in their study comparing zoledronic acid with pamidronate.

An observational study[166] reported on 177 patients receiving bisphosphonates over 13 months. They found the incidence of hypocalcaemia to be 15.8% in patients treated with zoledronic acid over this period. However this study included all grades of hypocalcaemia.

*Osteonecrosis of the jaw*

The rates of ONJ in the denosumab RCT were low and similar between the denosumab group and the zoledronic acid group (2.0% (20/1020) versus 1.4% (14/1013) ($p = 0.39$).[31] The cumulative incidence of ONJ in the denosumab and zoledronic acid groups, respectively, was 0.8% and 0.5% at 1 year, 1.9% and 1.2% at 2 years, and 2.0% and 1.4% at 3 years.[31] Stopeck and colleagues[31] reported that as of February 2010, 10 (50%) of denosumab-treated patients and six (43%) zoledronic acid–treated patients had resolution of the ONJ event; 10 (50%) of denosumab-treated patients and nine (64%) of the zoledronic acid–treated patients reported local infection; and seven patients in each group (35%, denosumab; 50%, zoledronic acid) reported undergoing limited surgical procedures such as debridement and sequestrectomy.

None of the other RCTs or observational studies reported ONJ.

*Renal toxicity*

In the denosumab RCT, a statistically significant lower rate of adverse events potentially associated with renal impairment occurred in the denosumab group compared with the zoledronic acid group (4.9% (50/1020) versus 8.5% (86/1013) respectively ($p = 0.001$).[31] Stopeck and colleagues[31] also reported that the rates of severe, and serious adverse events associated with renal impairment were also lower for denosumab compared with zoledronic acid (0.4% versus 2.2%, and 0.2% versus 1.5% respectively). The incidence of renal adverse events among patients with baseline renal clearance $\leq$ 60 mL/ min was also lower in the denosumab group (5.9%) than in the zoledronic acid group (20.0%), and a greater proportion of patients had decreases in their baseline creatinine clearance from $\geq$ 60 mL/min to < 60 mL/min with zoledronic acid (16.1%) compared with denosumab (12.7%).[31]

It should be noted that as zoledronic acid is contraindicated in patients with poor renal function, such patients were excluded from the denosumab study. The manufacturer stated that the incidence of renal toxicity observed in the denosumab group represented a background rate for patients with

advanced cancer, as such patients were predisposed to renal dysfunction, for example due to the use of nephrotoxic drugs.(manufacturer submission).

Rosen and colleagues[131] reported that there was no significant difference in renal safety profiles between the 4 mg zoledronic acid group and the 90 mg pamidronate group. After 25 months, a change of more than 0.5 mg/dL from baseline creatinine, had occurred in 7.7% of patients in the zoledronic acid group and 6.0% of patients in the pamidronate group.[131]

Kohno and colleagues[102] stated that there was no evidence of decreased renal function among patients in either group. In the zoledronic acid group, mean serum creatinine was 0.79 mg/dL at baseline and 0.78 mg/dL at end of study while in the placebo group it was 0.79 and 0.85 mg/dL. One patient in the zoledronic acid group had a notable serum creatinine increase (2.0 mg/dL) from a baseline of 1.3 mg/dL compared with seven patients in the placebo group. No patient in the zoledronic acid group developed a CTCAE grade 3 or 4 serum creatinine increase, whereas one patient in the placebo experienced such an event.[102]

*Acute phase reactions*

Acute phase reactions encompass flu-like syndrome including pyrexia, chills, flushing, bone pain, arthralgias and myalgias.[31] Stopeck and colleagues[31] reported that acute-phase reactions occurring within the first three days after treatment were 2.7 times more common in the zoledronic acid group than the denosumab group (27.3% (277/1013) versus 10.4% (106/1020) respectively). In the manufacturer's submission, serious adverse events of acute phase reactions within three days of first dose were [redacted] in the zoledronic acid group and [redacted] in the denosumab group.

*Other adverse events*

Table 14 shows, for the denosumab RCT, rates of a number of selected other adverse events, including those leading to treatment discontinuation, CTCAE grade 3 or 4 events, serious and fatal adverse events. The rates for both groups were broadly similar.

**Table 14 Selected other adverse events**

| **Adverse event** | **Denosumab (n=1020)** | **Zoledronic acid (n=1013)** |
|---|---|---|
| **AE leading to treatment discontinuation** | 98 (10%) | 125 (12%) |
| **CTCAE ≥ grade 3 AE** | 609 (60%) | 635 (63%) |
| **Serious AE** | 453 (44%) | 471 (47%) |

Source: Stopeck 2010

**Notes:**

1. AE, adverse event, CTCAE, Common Terminology Criteria for Adverse Events (version 3.0).

For details of all other adverse extracted from the RCTs meeting the review's inclusion criteria and also adverse events extracted from a number of observational studies identified, see Appendix 10.

### *6.2.10 Network meta-analysis*

A network meta-analysis (NMA) was undertaken by the assessment group (AG NMA). A NMA was also presented within the manufacturer's submission (MS NMA). The AG included four studies[30,31,103,104] and the MS NMA included 11 studies. Table 15 shows the comparisons and outcomes reported by the AG and MS NMAs.

**Table 15 Assessment group's NMA compared with the manufacturer's NMA**

| Comparisons | Time to first SRE | Time to first and subsequent SRE | SMR/SMPR | Proportion of patients with on study SRE |
|---|---|---|---|---|
| **Denosumab versus zoledronic acid** | AG +MS | AG +MS | AG +MS | AG |
| **Denosumab versus placebo** | AG +MS | AG +MS | AG +MS | AG |
| **Denosumab versus pamidronate** | AG +MS | AG +MS | AG +MS | Neither |
| **Zoledronic acid versus placebo** | AG +MS | AG +MS | AG +MS | AG |
| **Denosumab versus ibandronic acid** | MS | MS | Neither | Neither |

To convert time to event analysis, the statistical technique outlined by Tierney[70] was used. Whilst this is an accepted method of converting to HRs there are assumptions made and this adds a further layer to the uncertainties of the NMA. This was performed for time to first SRE for Kohno[102] (zoledronic acid versus placebo, HR 0.56 95%CI 0.36 to 0.85) and Rosen[104] (zoledronic acid versus pamidronate, HR 0.97, 95%CI 0.78 to 1.20). Conversion of Kohno[102] was straightforward using the number of observed events and p-value between groups. Conversion of Rosen[104] involved combining the lytic and non-lytic Kaplan-Meier curves.[110] The number of patients without an SRE at each time point and number at risk were then used to produce a hazard ratio. The HR calculated by the AG and

manufacturer were the same for Kohno,[102] but different for Rosen.[104] It is unclear what the precise method was that was used by the manufacturer to calculate the HR for the Rosen study.

The manufacturer included 11 studies in the NMA. Five studies were considered too heterogeneous by the AG for the reasons outlined below in Table 16. One study was not included in the AG NMA because it was non-English language (French). The AG used pooled results of two studies,[103] whereas the MS used unpooled studies.[108,116]

**Table 16 Reasons for exclusion of studies from the assessment group's NMA**

| Study | Reason that AG considered study too heterogeneous |
|---|---|
| **Heras 09[74]** | Different definition of SRE (includes change in anti-neoplastic medications) |
| **Body 03[71]** | Different definition of SRE (excludes spinal cord compression) |
| **Paterson 93[76]** | Different definition of SRE (excludes surgery and spinal cord compression) |
| **Kristensen 99[75]** | Different definition of SRE (includes HCM, excludes need for surgery and spinal cord compression) |
| **Body 04[72] [Tripathy 03[167]]** | Different definition of SRE (excludes spinal cord compression) |

**Notes:**

1. HCM, hypercalcaemia of malignancy.

*Time to first on-study SRE*

The results from the AG and MS NMA are shown below in Table 17.

**Table 17 Time to first on-study SRE**

| Comparison | AG NMA HR (95% CI) | MS NMA HR (95% CI) |
|---|---|---|
| **Denosumab versus zoledronic acid** | 0.81 (0.78 to 0.83) | [redacted] |
| **Denosumab versus pamidronate** | 0.89 (0.86 to 0.93) | [redacted] |
| **Denosumab versus placebo** | 0.48 (0.46 to 0.51) | [redacted] |
| **Zoledronic acid versus placebo** | 0.57 (0.55 to 0.59) | [redacted] |
| **Denosumab versus ibandronic acid** | Not performed | [redacted] |

In both the AG NMA and MS NMA time to first SRE favoured denosumab compared with zoledronic acid, pamidronate and placebo. In the AG NMA the difference was statistically significant, [redacted]

[redacted]. The indirect result for denosumab versus zoledronic acid is different from the direct result because within a NMA baseline risk of zoledronic acid is changed because of the other studies included. The AG did not compare denosumab with ibandronic acid, since they considered the studies too heterogeneous to provide meaningful results. [redacted]

*Risk of first-and-subsequent on-study SRE*

The results for risk of developing first-and-subsequent on-study SREs are provided below in Table 18.

**Table 18 Risk of first-and-subsequent on-study SRE**

| **Comparison** | **AG NMA**<br>**RR (95% CI)** | **MS NMA**<br>**RR (95% CI)** |
|---|---|---|
| **Denosumab versus zoledronic acid** | 0.75 (0.73 to 0.76) | [redacted] |
| **Denosumab versus pamidronate** | 0.57 (0.55 to 0.59) | [redacted] |
| **Denosumab versus placebo** | 0.42 (0.41 to 0.43) | [redacted] |
| **Zoledronic acid versus placebo** | 0.55 (0.54 to 0.56) | [redacted] |
| **Denosumab versus ibandronic acid** | Not performed | [redacted] |

Risk of first-and-subsequent SRE favoured denosumab compared with zoledronic acid, pamidronate or placebo in both the AG NMA and MS NMA. In the AG NMA the difference was statistically significant, [redacted]

*Skeletal morbidity rate (SMR) and skeletal morbidity period rate (SMPR)*

The AG did not have access to SMPR for denosumab compared with zoledronic acid and were therefore unable to perform this comparison (Table 19).

**Table 19 Skeletal morbidity rate and skeletal morbidity period rate**

| Comparison | SMR | | SMPR |
|---|---|---|---|
| | **AG NMA Rate Ratio (95% CI)** | **MS NMA Rate Ratio (95% CrI)** | **MS NMA Rate Ratio (95% CrI)** |
| **Denosumab versus zoledronic acid** | 0.90 (0.67 to 1.09) | [redacted] | [redacted] |
| **Denosumab versus pamidronate** | 0.73 (0.41 to 1.06) | [redacted] | [redacted] |
| **Denosumab versus placebo** | 0.47 (0.25 to 0.67) | [redacted] | [redacted] |
| **Zoledronic acid versus placebo** | 0.52 (0.32 to 0.70) | [redacted] | [redacted] |
| **Denosumab versus ibandronic acid** | Not performed | [redacted] | [redacted] |

The SMR in both the AG NMA and MS NMA favour denosumab. There was a statistically significant difference for denosumab compared with placebo (AG NMA), zoledronic acid versus placebo (AG NMA) [redacted]

*Proportion of patients with on-study SRE*

The AG undertook a NMA comparing the proportion of patients with an on-study SRE (Table 20). This is a less informative outcome since it does not differentiate between length of study. However the AG judged the study lengths to be similar enough to be included within the NMA. It also provided an opportunity to compare interventions by individual SRE.

**Table 20 Proportion of patients with an on-study SRE**

| | Any SRE OR (95%CI) | Pathological fracture OR (95%CI) | Radiation to bone OR (95%CI) | Surgery to bone OR (95%CI) | Spinal cord compression OR (95%CI) |
|---|---|---|---|---|---|
| **Denosumab versus zoledronic acid** | 0.77 (0.11 to 4.86) | 0.80 (0.06 to 10.11) | 0.72 (0.06 to 8.62) | 1.03 (0.08 to 13.15) | 1.30 (0.10 to 17.94) |
| **Denosumab versus placebo** | 0.36 (0.03 to 3.96) | 0.42 (0.01 to 15.96) | 0.31 (0.01 to 12.48) | 0.38 (0.00 to 30.47) | 0.34 (0.01 to 14.73 |
| **Zoledronic acid versus placebo** | 0.47 (0.09 to 2.23) | 0.53 (0.04 to 6.89) | 0.43 (0.03 to 6.28) | 0.37 (0.01 to 12.97) | 0.26 (0.02 to 3.89) |

Compared to zoledronic acid denosumab non-significantly reduced the risk of any SRE, pathological fracture and radiation to bone. There was a non-significant increase in spinal cord compression compared with zoledronic acid. Compared to placebo both denosumab and zoledronic acid non-significantly reduced the risk of each individual SRE. It should be noted that none of the above results were statistically significant and the NMA is not sufficiently powered to detect differences. Individual SREs should not be compared to each other, for example comparing the effectiveness of an intervention to prevent pathological fractures compared with spinal cord compression, because of the low numbers of events.

### 6.3 Summary

Only one study, by Stopeck and colleagues[31] was identified comparing denosumab with the primary comparator zoledronic acid. Three other studies contributed data to the indirect comparisons of denosumab versus BSC undertaken by the Assessment Group (these three studies were also included in the MS NMA) and were therefore also reported in this chapter. Kohno and colleagues[102] compared zoledronic acid with placebo, Rosen and colleagues[104] compared zoledronic acid with pamidronate and Lipton and colleagues[103] compared pamidronate with placebo. All studies were generally of good quality. In terms of generalisability, all studies were multicentre and all apart from Kohno 2005[102] were international. In the Kohno 2005 study[102] the patients were all Japanese and all had osteolytic lesions. The Stopeck study[31] was the largest, randomising 2046 patients, although only [redacted] were from the UK. All participants in this study had advanced breast cancer with ≥ 1 bone metastases, ECOG

status ≤ 2 and a life expectancy of ≥ 6 months. Patients with severe renal impairment, current or prior bisphosphonate treatment, nonhealed dental/oral surgery or prior malignancy within three years before randomisation were excluded. The study was powered to detect both non-inferiority and superiority with respect to time to first, and risk of first-and-subsequent, on-study SREs.

The study by Stopeck and colleagues[31] reported a statistically significant difference in favour of denosumab compared with zoledronic acid in both the median time to first on-study SRE (not yet reached versus 26.4 months), most of which were radiation to bone or pathological fractures, and the risk of developing first-and subsequent on-study SREs.

In the study by Kohno and colleagues,[102] the median time to first on-study SRE was significantly longer in the zoledronic acid group compared with the placebo group (not reached versus around 12 months), while the risk of developing multiple SREs was 41% lower in the zoledronic acid group. Likewise, in the study by Lipton and colleagues[103] the time to first on-study SRE was significantly longer in the pamidronate group compared with the placebo group (12.7 versus 7 months). In the study by Rosen and colleagues[104] comparing zoledronic acid with pamidronate the median time to first on-study SRE was broadly similar (around 11.6 versus 12.2 months) while the risk of developing multiple SREs was 20% lower in the zoledronic acid group.

In the denosumab RCT [redacted]. Kohno and colleagues reported that 2.6% of the zoledronic acid group and 8.8% of the placebo group experienced hypercalcaemia.

In the denosumab study median overall survival was [redacted] months for the denosumab group versus [redacted] for the zoledronic acid group. The study by Lipton and colleagues reported that median overall survival was slightly longer in the pamidronate group compared with the placebo group (19.8 versus 17.8 months).

Denosumab delayed the time to development of moderate or severe pain by more than four months compared with zoledronic acid (around 10.5 versus 6.3 months). Lipton and colleagues[103] reported that the mean pain score decreased significantly in the pamidronate group (-0.07) compared with the placebo group (1.14). The FACT quality of life scores were similar between the denosumab and zoledronic acid groups and likewise there were no notable differences between the groups in terms of EQ-5D. Lipton and colleagues,[103] using the Spitzer quality of life index, noted that from baseline to the last visit quality of life worsened in both the pamidronate group (-1.80) and the placebo group (-2.13).

In terms of adverse events, slightly more hypocalcaemia events occurred in the denosumab group compared with the zoledronic acid group (5.5% versus 3.4%), likewise for ONJ (2.0% versus 1.4%), there was a statistically significant lower rate of adverse events potentially associated with renal impairment (4.9% versus 8.5%), while fewer patients in the denosumab group experienced acute phase reactions (10.4% versus 27.3%). The rates for adverse events leading to treatment discontinuation, CTCAE grade 3 or 4, or serious adverse events were broadly similar between the denosumab and zoledronic acid groups.

In the study by Kohno and colleagues,[102] 39% of the zoledronic acid group and 7% of the placebo group experienced grade 1 hypocalcaemia. Rosen and colleagues[104] reported that there was no significant difference in renal safety profiles between the zoledronic acid and pamidronate groups, while in the study by Kohno and colleagues[102] there was no evidence of decreased renal function in either the zoledronic acid or placebo groups.

The AG NMA included fewer trials than the MS NMA, improving homogeneity, however this reduced the number of outcomes and available comparisons. The MS NMA included six more studies. It is the opinion of the AG that inclusion of these six additional studies introduced significant methodological heterogeneity to the NMA. All treatment effects were in the same direction in both AG NMA and MS NMA. The results from the AG NMA show that denosumab compared with zoledronic acid, placebo or pamidronate significantly delayed the time to first SRE and significantly reduced the risk of first-and-subsequent SRE, and that denosumab compared with placebo significantly reduced the SMR. [redacted] The proportion of SREs was non-significantly reduced in all SRE types, except for spinal cord compression. However these results are subject to considerable uncertainty and should be interpreted with caution.

# 7 RESULTS - PROSTATE CANCER

## 7.1 Quantity of research available

### *7.1.1 Number and type of studies included*

See Section 6.1.1 for the flow diagram outlining the screening process for the overall review.

The primary comparator for denosumab was considered to be best supportive care (BSC), as in the NICE guideline on the diagnosis and treatment of prostate cancer the use of bisphosphonates to prevent or reduce the complications of bone metastases in men with hormone-refractory prostate cancer is not recommended.[46] BSC was defined as including palliative radiotherapy and analgesics. As the guideline states that bisphosphonates for pain relief may be considered when other treatments (including analgesics and palliative radiotherapy) have failed, bisphosphonates were considered as a secondary comparator in relation to this group of patients.

No RCTs were identified comparing denosumab with BSC. One RCT (six reports[29,123,125,126,128,130]) was identified comparing denosumab with the bisphosphonate zoledronic acid. The primary published report for this study was considered to be by Fizazi and colleagues.[29] One study (nine reports[19,118-122,124,127,129]) comparing zoledronic acid with placebo was identified and this study also contributed data to the indirect comparison of denosumab versus BSC. The primary report for this study was considered to be the 2002 paper by Saad and colleagues.[118]

### *7.1.2 Number and type of studies excluded*

See section 6.1.2 for information on studies that were excluded from the review and Appendix 5 for a list of these studies along with the reasons for their exclusion. These studies were excluded because they failed to meet one or more of the inclusion criteria in terms of types of study, participants, intervention or outcomes reported.

### *7.1.3 Characteristics of the included studies*

Appendix 8 shows the characteristics of the included studies. Table 21 shows summary information for the two studies that provided direct evidence for denosumab or were included in the network meta-analysis (NMA).

**Table 21 Characteristics of the studies included in the network meta-analysis**

| | Fizazi 2011[29] | | Saad 2002[118] | |
|---|---|---|---|---|
| | **Denosumab** | **ZA** | **ZA** | **Placebo** |
| **Randomised** | 950 | 951 | 214 | 208 |
| **Age** | 71 (64-77) | 71 (66-77) | 71.8 (7.9) | 72.2 (8.0) |
| **Ethnicity:** | | | | |
| ***White*** | 829 (87%) | 810 (85%) | 178 (83%) | 173 (83%) |
| ***Other*** | 121 (135) | 141 (15%) | 36 (17%) | 35 (17%) |
| **ECOG status 0-1** | 882 (93%) | 886 (93%) | 197 (92%) | 190 (91%) |
| **Time from diagnosis, months:** | | | | |
| ***Of prostate cancer*** | 37.5 (18.1-75.4) | 41.2 (18.3-82.0) | 62.2 ± 43.5 | 66.6 ± 46.9 |
| ***Of bone metastases*** | 3.94 (1.22-15.67) | 5.19 (1.31-16.10) | 23.8 ± 26.1 | 28.4 ± 30.7 |
| **Previous SREs** | 232 (24%) | 231 (24%) | 66 (31%) | 78 (38%) |

**Notes:**

1. ZA, zoledronic acid; SRE, skeletal related event.
2. Age. Fizazi[29] reported median (interquartile range), Saad[118] reported mean (standard deviation).
3. Time from diagnosis. Fizazi[29] reported median (interquartile range), Saad[118] reported mean (standard deviation) and also median; for time since diagnosis this was 51.8 months for denosumab and 56.9 months for placebo; for time since first bone metastases this was 16.1 months for denosumab and 17.8 months for placebo.

The study by Fizazi and colleagues[29] was undertaken between May 2006 and October 2009 and enrolled men aged 18 years or older with confirmed prostate cancer and at least one bone metastasis, from 342 centres in 39 countries. However only [redacted] of patients were from the UK.(manufacturer submission) Exclusion criteria included creatinine clearance < 0.5 mL/s, current or previous treatment with intravenous bisphosphonate or oral bisphosphonate for bone metastases, planned radiation therapy or surgery to bone, life expectancy < 6 months, current or previous osteonecrosis or osteomyelitis of the jaw or any planned invasive dental procedure during the study. Patients received a subcutaneous injection of 120 mg denosumab and an intravenous infusion of placebo or an intravenous infusion of 4 mg zoledronic acid and a subcutaneous injection of placebo every four weeks. The study was powered to detect both non-inferiority and superiority with respect to time to first on-study SRE (primary outcome), and time to first-and-subsequent SRE. Follow-up was 41 months for the blinded treatment phase. The study was funded by Amgen.

The study by Saad and colleagues[118] was undertaken between June 1998 and January 2001 and enrolled prostate cancer patients with a documented history of bone metastases, from more than 136 centres in the USA, Europe, South America and Australasia. Patients received 4 mg zoledronic acid or placebo every three weeks (a third arm in which 221 patients were assigned to an initial dose of 8 mg per week was not considered to meet our inclusion criteria). All patients also received a 500 mg calcium supplement and 400–500 IU of vitamin D daily. Pain management, including analgesics, radiation therapy, or other treatment, was at the discretion of the treating physician. The primary outcome was the proportion of patients having at least one SRE. Follow-up was 15 months (with an extension phase to 24 months). The study was funded by Novartis.

### *7.1.4 Quality of the included studies*

Table 22 shows the results of the risk of bias assessment for the studies by Fizazi and colleagues[29] and Saad and colleagues.[118]

**Table 22 Results of the risk of bias assessment**

| | **Fizazi 2011[29]** | **Saad 2002[118]** |
|---|---|---|
| **Adequate sequence generation** | Yes | Yes |
| **Adequate allocation concealment** | Yes | Yes |
| **Blinding** | Yes | Yes |
| **Incomplete outcome data addressed** | Yes | Yes |
| **Free of selective reporting** | Yes | Yes |

Both studies were good quality studies with low risk of bias as assessed against the criteria in the table. The study by Fizazi and colleagues[29] employed computer-generated randomisation, with an interactive voice response system used to assign patients (1:1 ratio) to treatment. Patients, study staff and investigators were masked to treatment assignment throughout the primary analysis period. Both primary and secondary efficacy endpoints included all randomised patients, irrespective of administration of study treatments (intention to treat), while the safety dataset included all patients from the full analysis set who received at least one dose of study treatment. There was adequate description of withdrawals and losses to follow-up, and all of the prespecified outcomes were reported

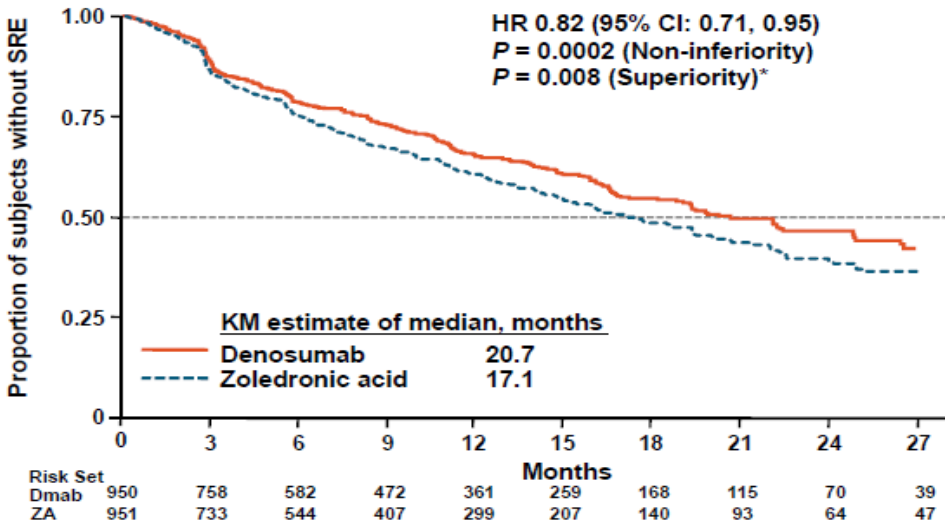
The study by Saad and colleagues[118] employed a computer-generated list of randomisation numbers to assign patients. Treatment assignments were revealed to study personnel and any other persons involved in study conduct or monitoring only after the last patient had completed the last study visit. The study was double blind, patients lost to follow-up were described and all of the prespecified outcomes were reported.

## 7.2 Assessment of effectiveness

### *7.2.1 Time to first on-study SRE*

The study by Fizazi and colleagues[29] reported a statistically significant difference in favour of denosumab compared with zoledronic acid in the median time to first on-study SRE (20.7 versus 17.1 months, HR 0.82 (95% CI 0.71 to 0.95), p = 0.0002), reducing the risk of this event by 18% compared with zoledronic acid. Figure 6 shows the Kaplan-Meier estimates of the time to the first on-study SRE. The manufacturer's submission reported that denosumab reduced the risk of a symptomatic SRE by [redacted] and reduced the proportion of patients with symptomatic SREs (25% versus [redacted].(manufacturer submission)

**Figure 6 Kaplan-Meier estimates of time to first on-study SRE**




Source: manufacturer submission.

The study by Saad and colleagues[118] reported a statistically significant difference in favour of zoledronic acid compared with placebo in the median time to first on-study SRE (488 versus 321 days, HR 0.68 (95% CI 0.51 to 0.91), p = 0.009), reducing the risk of this event by 32% compared with placebo.

*SRE by type*

Neither study reported the time to first SRE for individual SREs.

Table 23 shows the distribution of first on-study SRE by type of SRE in the study by Fizazi and colleagues.[29] The distribution of type of SRE was similar across the treatment groups, with radiation to bone and pathological fracture being the most commonly occurring.

**Table 23 Patients with first on-study SRE by type**

| | Denosumab (n=950 randomised) | Zoledronic acid (n=951 randomised) |
|---|---|---|
| | **Number of events (%)** | **Number of events (%)** |
| **Overall** | 341 (100%) | 386 (100%) |
| **Radiation to bone** | 177 (51.9%) | 203 (52.6%) |
| **Pathological fracture** | 137 (40.2%) | 143 (37.1%) |
| **Spinal cord compression** | 26 (7.6%) | 36 (9.3%) |
| **Surgery to bone** | 1 (0.3%) | 4 (1.0%) |

Source: Fizazi 2011[29]

Saad and colleagues[118] did not report this outcome.

*Prior history of SRE*

The manufacturer's submission reported time to first on-study SRE by prior history of SRE for study 103 (Table 24). This showed a statistically significant difference in favour of denosumab for those patients with no prior SRE, while for those with a prior SRE [redacted]. Covariate analysis showed that patients with a prior SRE history had an increased risk of [redacted] compared with those without an SRE history.

**Table 24 Time to first on-study SRE by prior history of SRE**

| | | Denosumab | Zoledronic acid |
|---|---|---|---|
| **Overall** | **Number** | 950 | 951 |
| | **HR (95% CI)** | 0.82 (0.71, 0.95) | |
| | **p-value** | 0.008 | |
| **No prior SRE** | **Number** | 718 | 720 |
| | **HR (95% CI)** | 0.80 (0.67, 0.95) | |
| | **p-value** | 0.011 | |
| **Prior SRE** | **Number** | 232 | 231 |
| | **HR (95% CI)** | [redacted] | |
| | **p-value** | [redacted] | |
| **Covariate effect** | **Pt estimate (95% CI)** | [redacted] | |
| | **P value** | [redacted] | |

Source: Manufacturer submission

**Notes:**

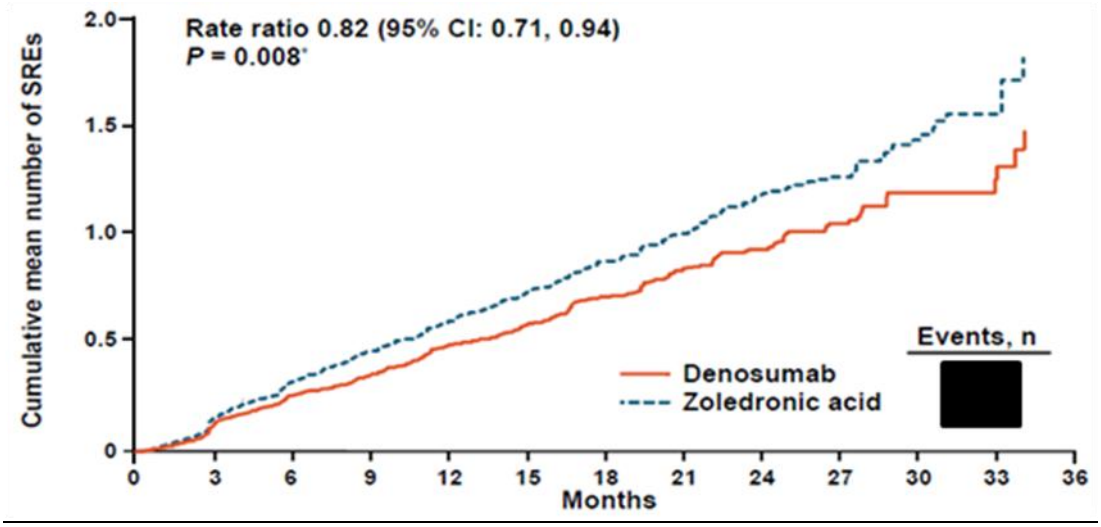
1. Hazard ratio (HR) based on the Cox proportional hazards model with treatment groups as independent variables and stratified by the randomisation stratification factors.

Saad and colleagues[118] reported that the median time to first on-study SRE for those with a previous SRE (n=144) was 361 days for the zoledronic acid group compared with 258 days for the placebo group (p=0.066), while for those with no previous SRE (n=277) it was 499 days for the zoledronic acid group and 337 days for the placebo group (p=0.065).[120]

### *7.2.2 Risk of first-and-subsequent on-study SREs*

The study by Fizazi and colleagues[29] reported a statistically significant difference in favour of denosumab compared with zoledronic acid in the risk of developing first-and-subsequent on-study SREs (RR 0.82 (95% CI 0.71 to 0.94), p = 0.004, adjusted (for multiplicity) p=0.008). Figure 7 shows the cumulative mean number of SREs (multiple event analysis).

**Figure 7 Cumulative mean number of SREs (multiple event analysis)**




Source: manufacturer submission.

Saad and colleagues[118] reported a statistically significant difference in favour of zoledronic acid compared with placebo in the risk of developing first-and-subsequent on-study SREs (RR 0.64 (95% CI not reported), p=0.002.

*SRE by type*

Neither study reported risk of first-and-subsequent on-study SRE by type of SRE.

The manufacturer's submission reported the distribution of first-and-subsequent on-study SREs by type of SRE in the denosumab RCT (study 103) (Table 25). As for first on-study SRE by type, the distribution of type of SRE was similar across the treatment groups, with radiation to bone and pathological fracture again the most commonly occurring.

**Table 25 Distribution of first-and-subsequent SRE by type – with 21 day window**

| | **Denosumab (n=950 randomised)** | **Zoledronic acid (n=951 randomised)** |
|---|---|---|
| | **Number of events (%)** | **Number of events (%)** |
| **Total confirmed events** | [redacted] | [redacted] |
| **Radiation to bone** | [redacted] | [redacted] |
| **Pathological fracture** | [redacted] | [redacted] |
| **Spinal cord compression** | [redacted] | [redacted] |
| **Surgery to bone** | [redacted] | [redacted] |

Source: manufacturer submission

*Prior history of SRE*

The manufacturer's submission reported risk of developing first-and-subsequent on-study SREs by prior history of SRE for study 103 (Table 26). [redacted] Covariate analysis as presented in the manufacturer's table showed that patients with a prior SRE history had an increased risk of [redacted] compared with those without an SRE history (although in the text the manufacturer reported that the covariate effect was [redacted] (increased risk of [redacted])).

**Table 26 Risk of first-and-subsequent on-study SREs by prior history of SRE**

| | | Denosumab | Zoledronic acid |
|---|---|---|---|
| **Overall** | **Number** | 950 | 951 |
| | **RR (95% CI)** | 0.82 (0.71, 0.94) | |
| | **p-value** | 0.0044 | |
| **No prior SRE** | **Number** | 718 | 720 |
| | **RR (95% CI)** | [redacted] | |
| | **p-value** | [redacted] | |
| **Prior SRE** | **Number** | 232 | 231 |
| | **RR (95% CI)** | [redacted] | |
| | **p-value** | [redacted] | |
| **Covariate effect** | **Pt estimate (95% CI)** | [redacted] | |
| | **p value** | [redacted] | |

Source: manufacturer submission

**Notes:**

1. Rate ratio (RR) based on the Anderson-Gill model stratified by the randomised stratification factors.

Saad and colleagues reported that among the 144 patients with an SRE before study entry, zoledronic acid significantly reduced the risk of SREs by 40% compared with placebo (RR 0.60, p = 0.028, and among the 277 patients without an SRE before study entry, zoledronic acid significantly reduced the overall risk of SREs by 33% compared with placebo (RR 0.67, p = 0.027).[120]

### *7.2.3 Skeletal morbidity rate*

The skeletal morbidity rate (SMR) is defined as the ratio of the number of SREs per patient divided by the patient's time at risk. Information on this outcome for the denosumab RCT was reported in the manufacturer's submission, which stated that for the SMR calculations a 21-day event window was used for counting on-study SREs, so that any event occurring within 21 days of a previous event was not counted as a separate on-study SRE.

The manufacturer's submission reported that in study 103 the annual SMR was [redacted] with denosumab compared with zoledronic acid [redacted]. Saad and colleagues[118] reported that the mean SMR for all SREs combined and for each individual type of SRE was lower for patients who received zoledronic acid than for those who received placebo.

*SRE by type*

The manufacturer's submission did not report SMR by type of SRE.

Table 27 shows the SMR by type of SRE for the study by Saad and colleagues.[118]

**Table 27 Skeletal morbidity rate up to month 15**

| | ZA (n=214) | Placebo (n=208) | p value |
|---|---|---|---|
| **All SREs** | 0.80 (0.57, 1.03) | 1.49 (1.03, 1.94) | 0.006 |
| **Pathological fractures** | 0.21 (0.11, 0.31) | 0.45 (0.27, 0.63) | 0.009 |
| **Radiation therapy to bone** | 0.44 (0.27, 0.60) | 0.88 (0.48, 1.28) | 0.084 |
| **Surgery to bone** | 0.03 (0.00, 0.07) | 0.06 (0.01, 0.11) | 0.509 |
| **Spinal cord compression** | 0.14 (0.00, 0.28) | 0.23 (0.04, 0.42) | 0.247 |

Source: Saad 2002[118]

**Notes:**

1. Data are mean number of SREs per patient year (95% CI).

*Prior history of SRE*

SMR by prior history of SRE was not reported for the denosumab RCT.

Saad and colleagues reported that the mean on-study skeletal morbidity rate (SREs per year), for those patients with a previous SRE (n=144) was 0.8 for zoledronic acid compared with 2.3 for placebo (p = 0.036), while for those with no previous SRE it was 0.77 for zoledronic acid and 0.98 for placebo (p = 0.06).[120]

### *7.2.4 Incidence of SREs*

In the denosumab RCT (study 103) 780 SREs occurred in 1045 patient-years in the denosumab arm and 943 occurred in 996 patient-years in the zoledronic acid arm, with the number needed to treat (NNT) analysis showing that compared with zoledronic acid, treatment of five patients with denosumab would prevent an additional SRE (first or subsequent) per year.[125]

The manufacturer's submission reported an annualised SRE rate based on the number of SREs observed in each treatment arm divided by the number of patient-years for each treatment arm and reported this outcome both with and without a 21-day event window.

Table 28 shows the annualised SRE rate both with and without the 21-day window for study 103. The manufacturer's submission reported that the primary analysis of annualised SRE rates was based on all SREs reported in each arm of the study (calculated without a 21-day window). Subsequently, a post-hoc analysis of the annualised SRE rate applying the trial-defined 21-day window for SREs was conducted. Both analyses show that the annualised SRE rate was lower in patients receiving denosumab compared with those receiving zoledronic acid.

**Table 28 Annualised SRE rate in study 103**

| | **Denosumab (n=950)** | **Zoledronic acid (n=951)** |
|---|---|---|
| **Annualised SRE rate per patient** | | |
| Subject years | [redacted] | [redacted] |
| **Without 21-day window** | | |
| Number of events | [redacted] | [redacted] |
| Annualised rate | [redacted] | [redacted] |
| **With 21-day window** | | |
| Number of events | [redacted] | [redacted] |
| Annualised rate | [redacted] | [redacted] |

Source: manufacturer submission.

In the study by Saad and colleagues[118] statistically significantly fewer patients in the zoledronic acid group compared with the placebo group experienced at least one SRE (33.2% (71/214) versus 44.2% (92/208) respectively, p = 0.021.

*SRE by type*

Incidence of SREs by type of SRE was not reported for the denosumab RCT.

Table 29 shows the proportions of patients with different types of SRE for the study by Saad and colleagues.[118] More SREs occurred in the placebo group overall. The most frequently occurring SRE in both groups was radiation therapy to bone, followed by pathological fractures.

**Table 29 Proportions of patients with SREs up to month 15**

| | ZA (n=214) | Placebo (n=208) | p value |
|---|---|---|---|
| **All SREs** | 71 (33.2) | 92 (44.2) | 0.021 |
| **Pathological fractures** | 28 (13.1) | 46 (22.1) | 0.015 |
| **Radiation therapy to bone** | 49 (22.9) | 61 (29.3) | 0.136 |
| **Surgery to bone** | 5 (2.3) | 7 (3.4) | 0.514 |
| **Spinal cord compression** | 9 (4.2) | 14 (6.7) | 0.256 |

Source: Saad 2002[118]

**Notes:**

1. ZA, zoledronic acid.

- *Prior history of SRE*

Neither study reported incidence of SRE by prior history of SRE. However Saad and colleagues reported that for those with a previous SRE (n=144), the proportion of patients with ≥ 1 SRE while on study was 41% (27/66) for zoledronic acid compared with 51% (40/78 for placebo (p = 0.215), while for those with no previous SRE (n=277) this was 37% (54/147) for zoledronic acid compared with 47% (61/130) for placebo (p = 0.087).[120]

### *7.2.5 Prevention of hypercalcaemia*

In study 103, [redacted].(CSR 103)

Saad and colleagues[118] did not report hypercalcaemia.

### *7.2.6 Overall survival*

In the denosumab RCT, median overall survival was similar between the groups with a median overall survival of 19.4 months (95% CI 18.1 to 21.7) for the denosumab group compared with 19.8 months (95% CI 18.1 to 20.9) for the zoledronic acid group (HR 1.03, 95% CI 0.91 to 1.17, p=0.65).[29]

In the study by Saad and colleagues,[118] median survival was 546 days (around 18.2 months) for the zoledronic acid group and 464 days (around 15.5 months) for the placebo group (p = .091).

*Prior history of SRE*

Neither study reported overall survival by prior history of SRE.

### *7.2.7 Pain*

The manufacturer's submission stated that the denosumab RCT used the Brief Pain Inventory – Short Form (BPI-SF) which captures information on the intensity of pain (pain severity) and the degree to which pain interferes with function (pain interference) in patients with cancer. The BPI-SF scores range from 0 to 10, with a higher score indicating more severe pain (0 = no pain, 1-4 = mild pain, 5-6 = moderate pain and 7-10 = severe pain). Pain analyses included: evaluation of changes from baseline in BPI-SF worst pain score; evaluations of time to pain worsening, time to moderate or severe pain, or time to pain improvement; and the proportions of patients meeting these criteria.

The manufacturer's submission reported that denosumab delayed the time to development of moderate or severe pain in patients with no or mild pain at baseline by around one month compared with zoledronic acid (median 5.8 versus 4.9 months) although the difference was not statistically significant (HR 0.89, 95% CI 0.77 to 1.04; p = 0.1416).(manufacturer submission) Denosumab also significantly decreased the proportion of patients, with no/mild pain at base, who progressed to moderate or severe pain (relative decrease of [redacted] over 73 weeks). The median time to worsening pain (≥ 2 point increase from baseline in BPI-SF worst pain score) was comparable between denosumab and zoledronic acid ([redacted] versus [redacted] months, [redacted]. There was no significant difference in time to pain improvement (≥ 2 point decrease from baseline) between denosumab and zoledronic acid [redacted].(manufacturer submission)

There was no statistically significant difference at study end point or any study time point (19 study time points) in the use of strong analgesics.

The study by Saad and colleagues[118] also used the BPI instrument, with the pain score a composite of four pain scores (worst pain, least pain, average pain of the last seven days, and pain right now) and was the primary efficacy variable for the quality-of-life assessments. Saad and colleagues[118] reported that the mean pain scores increased from baseline in each group at every 3-month interval, apart from at three months where the zoledronic acid group had a slight decrease from baseline. The mean increase from baseline in pain score at 15 months was 0.58 (95% CI 0.29 to 0.87) for the zoledronic acid group compared with 0.88 (95% CI 0.61 to 1.15) for the placebo group (p = 0.134). Saad and colleagues[118] also reported that fewer patients in the zoledronic acid group experienced bone pain than in the placebo group (51% (108/214) versus 61% (127/208) respectively).

### *7.2.8 Health related quality of life*

*FACT*

The FACT-P questionnaire consists of the FACT-G questionnaire plus additional questions specific to prostate cancer. For each component of the FACT-P (FACT-G total score, FACT-P total score,

physical well-being domain, functional well-being domain, and Trial outcome index (TOI, a composite of the functional well-being domain, physical well-being domain, and the prostate cancer subscale), a higher score indicates better HRQOL.

Table 30 shows the change in FACT scores from baseline to week 73. [redacted] (CSR 103)

**Table 30 Change in FACT scores from baseline to week 73**

| | Denosumab (n=950) | | Zoledronic acid (n=951) | |
|---|---|---|---|---|
| | **Baseline Mean (SD)** | **Change from baseline to week 73** | **Baseline Mean (SD)** | **Change from baseline to week 73** |
| **FACT B/P total score** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Physical wellbeing** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Functional wellbeing** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Trial outcome index** | [redacted] | [redacted] | [redacted] | [redacted] |
| **FACT-G total score** | [redacted] | [redacted] | [redacted] | [redacted] |

Source: manufacturer's submission, appendix IV

Saad and colleagues[118] reported that the total FACT-G score decreased from baseline to the last measurement, with no statistically significant differences between the zoledronic acid and placebo groups.

*EQ-5D*

For both components of EQ-5D (the health index and the visual analogue scale (VAS)), a higher score indicates a more preferred health status. [redacted].(CSR 103)

Saad and colleagues[118] reported that the EQ-5D scores decreased from baseline to the last measurement, with no statistically significant differences between the zoledronic acid and placebo groups.

### *7.2.9 Adverse events related to treatment*

Data relating to adverse events were collected primarily from the included RCTs and supplementary data were included from observational studies where available.

*Hypocalcaemia*

The manufacturer's submission reported that hypocalcaemia events were mainly non-serious and transient and either resolved spontaneously or with calcium supplementation.(manufacturer submission) More hypocalcaemia adverse events occurred in the denosumab group than in the zoledronic acid group (13% (121/943) versus 6% (55/945) respectively), a statistically significant difference ($p < 0.0001$).[29] [redacted](manufacturer submission)

In the study by Saad and colleagues,[118] 1.9% (4/214) of patients in the zoledronic acid group experienced grade 3 or 4 hypocalcaemia compared with none in the placebo group.

*Osteonecrosis of the jaw*

In the denosumab RCT more patients in the denosumab group experienced ONJ events compared with the zoledronic acid group (2% (22/943) versus 1% (12/945), although the difference was not statistically significant ($p < 0.09$).[29] Of those, 17 (77%) on denosumab and ten (83%) on zoledronic acid had a history of tooth extraction, poor oral hygiene, or use of a dental appliance. Fizazi and colleagues[29] reported that by April 2010, surgical treatment for ONJ had been done in ten patients (45%) on denosumab who had limited surgery (debridement, sequestrectomy, or curettage) and two (9%) who had bone resection, whereas three patients (25%) on zoledronic acid had limited surgery and one (8%) had bone resection. They also reported that overall, resolution of osteonecrosis of the jaw, as defined by mucosal coverage, was recorded in four patients (18%) on denosumab and one patient (8%) on zoledronic acid.

ONJ was not reported by Saad and colleagues.[118]

The proportion of patients experiencing ONJ was slight lower than in observational studies (Appendix 11). Walter and colleagues[161] retrospectively studied patients prescribed bisphosphonates and found 18.6% of patients experienced ONJ (time at risk not reported). However three other observational studies found reported a cumulative incidence of 2.2% to 6.5% over 12-15 months.[62,138,145]

*Renal toxicity*

In the denosumab RCT, a similar rate of adverse events potentially associated with renal impairment occurred in the denosumab and zoledronic acid groups (15% (139/943) versus 16% (153/945) respectively).[29] The rates of serious adverse events associated with renal impairment were also similar (5.9% (56/943) versus 5.6% (53/945) respectively).(manufacturer submission) It should be noted that as zoledronic acid is contraindicated in patients with poor renal function, such patients were excluded from the trial. The manufacturer stated that the incidence of renal toxicity observed in the denosumab group represented a background rate for patients with advanced cancer, as such patients were predisposed to renal dysfunction, for example due to the use of nephrotoxic drugs.(manufacturer submission)

Saad and colleagues[118] reported that renal function deterioration occurred in 15.2% of patients who received zoledronic acid and 11.5% of those receiving placebo. They stated that Kaplan–Meier estimates of time to first renal function deterioration indicated a comparable relative risk between the groups, so that compared with the placebo group the zoledronic acid group had a relative risk of 1.07 (95% CI 0.46 to 2.47; p 0.882).[118]

Observational studies of zoledronic acid reported a higher incidence of renal toxicity. Oh and colleagues[153] found that 23.8% of patients experienced renal toxicity over 10 months and Bonomi and colleagues[138] found 6.5%. However these studies had a broader definition of renal toxicity than the RCTs.

*Acute phase reactions*

In the denosumab RCT, during the first 3 days of treatment, fewer patients in the denosumab group experienced symptoms associated with acute phase reactions compared with those in the zoledronic acid group (8% (79/943) versus 18% (168/945) respectively.[29]

Saad and colleagues[118] did not report this outcome.

*Other adverse events*

Table 31 shows, for the denosumab RCT, rates of a number of selected other adverse events, including those leading to treatment discontinuation, CTCAE grade 3 or 4 events, serious and fatal adverse events. The rates for both groups were broadly similar.

**Table 31 Selected other adverse events**

| Adverse event | Denosumab (n=943) | Zoledronic acid (n=945) | p value |
|---|---|---|---|
| **AE leading to treatment discontinuation** | 164 (17%) | 138 (15%) | 0.10 |
| **CTCAE grade 3 or 4 AE** | 678 (72%) | 628 (66%) | 0.01 |
| **Serious AE** | 594 (63%) | 568 (60%) | 0.20 |
| **Fatal AE** | 283 (30%) | 276 (29%) | 0.72 |

Source: Fizazi 2011[29]

**Notes:**

1. AE, adverse event, CTCAE, Common Terminology Criteria for Adverse Events (version 3.0).

Saad and colleagues[118] reported that similar proportions of patients who received zoledronic acid (9.8%) and placebo (10.1%) discontinued the study drug because of a serious adverse event.

The only other adverse event which appeared different between groups was anaemia (Appendix 11). [redacted] (CSR) In the study by Saad and

colleagues a greater number of patients in the zoledronic acid group experienced anaemia compared with the placebo group (26.6% versus 17.8%).[118] The clinical significance of this is unclear.

For details of all other adverse extracted from the RCTs meeting the review's inclusion criteria and also adverse events extracted from a number of observational studies identified, see Appendix 11

### *7.2.10 Network meta-analysis*

The assessment group (AG) and manufacturer (MS) performed an NMA for prostate cancer. Both NMAs included only two studies.[29,118] The definition of SRE differed between the studies. Saad[118] included change in anti-neoplastic medications. Therefore the results should be interpreted with caution. Table 32 shows the differences between the AG NMA and MS NMA.

**Table 32 Assessment group NMA compared with the manufacturer's NMA**

| | **Time to first SRE** | **Risk of first-and-subsequent SRE** | **SMR** | **Proportion of patients with on-study SRE** | |
|---|---|---|---|---|---|
| | | | | **All patients** | **Subgroup of patients with SRE at baseline** |
| **Denosumab versus zoledronic acid** | AG + MS | AG + MS | AG + MS | AG | AG |
| **Denosumab versus placebo** | AG + MS | AG + MS | AG + MS | AG | AG |
| **Zoledronic acid versus placebo** | AG + MS | AG + MS | AG + MS | AG | AG |

*Time to first SRE*

Results from the NMAs for time to first on-study SRE are shown in Table 33.

**Table 33 Time to first on-study SRE**

| | **AG NMA HR (95%CI)** | **MS NMA HR (95%CI)** |
|---|---|---|
| **Denosumab versus zoledronic acid** | 0.57 (0.54 to 0.59) | [redacted] |
| **Denosumab versus placebo** | 0.45 (0.43 to 0.48) | [redacted] |
| **Zoledronic acid versus placebo** | 0.66 (0.64 to 0.68) | [redacted] |

The NMA results from both the AG and MS show that time to first SRE favoured denosumab compared with zoledronic acid or placebo. The AG NMA found these differences to be statistically significant in favour of denosumab, [redacted].

*Risk of first-and-subsequent SREs*

The NMA results for risk of developing first-and-subsequent on-study SREs are shown in Table 34.

**Table 34 Risk of first-and-subsequent on-study SREs**

| | **AG NMA RR (95%CI)** | **MS NMA RR (95%CI)** |
|---|---|---|
| **Denosumab versus zoledronic acid** | 0.83 (0.81 to 0.85) | [redacted] |
| **Denosumab versus placebo** | 0.56 (0.54 to 0.58) | [redacted] |
| **Zoledronic acid versus placebo** | 0.69 (0.67 to 0.71) | [redacted] |

The NMA results show the risk of developing first-and-subsequent SREs favoured denosumab compared with zoledronic acid or placebo. The AG NMA found these differences to be statistically significant in favour of denosumab, [redacted].

*Skeletal morbidity rate (SMR)*

The NMA results for SMR are shown in Table 35.

**Table 35 Skeletal morbidity rate**

| | **AG NMA RR (95% CI)** | **MS NMA RR (95%CI)** |
|---|---|---|
| **Denosumab versus zoledronic acid** | 0.95 (0.46 to 1.47) | [redacted] |
| **Denosumab versus placebo** | 0.52 (0.07 to 0.82) | [redacted] |
| **Zoledronic acid versus placebo** | 0.54 (0.11 to 0.83) | [redacted] |

The AG NMA found a non-significant difference in favour of denosumab compared with zoledronic acid and a significant difference in favour of denosumab compared with placebo, while there was a statistically significant difference in favour zoledronic acid compared with placebo. [redacted]

*Proportion of patients with on-study SRE*

The AG compared the proportion of patients with an on-study SRE for individual SREs and with a subgroup with a SRE history. This outcome does not differentiate between time on study and therefore the results should be interpreted with caution. However it provides an opportunity to indirectly compare SRE types and SRE history.

Denosumab non-significantly favoured zoledronic acid and placebo throughout. Due to the small numbers however these results should not be used to compare the relative effectiveness of denosumab for preventing individual SRE types.

**Table 36 Proportion of patients with an on-study SRE**

| | Any SRE OR (95%CI) | Pathological fracture OR (95%CI) | Radiation to bone OR (95%CI) | Surgery to bone OR (95%CI) | Spinal cord compression OR (95%CI) | No prior SRE OR (95%CI) | Prior SRE OR (95%CI) |
|---|---|---|---|---|---|---|---|
| **Denosumab versus zoledronic acid** | 0.81 (0.07 to 10.40) | 0.91 (0.07 to 12.06) | 0.79 (0.06 to 10.16) | 0.58 (0.04 to 7.34) | 0.73 (0.06 to 9.65) | 0.82 (0.06 to 10.01) | 0.81 (0.07 to 10.27) |
| **Denosumab versus placebo** | 0.53 (0.01 to 18.80) | 0.48 (0.01 to 18.46) | 0.57 (0.02 to 19.20) | 0.39 (0.01 to 15.95) | 0.44 (0.01 to 16.32) | 0.53 (0.01 to 19.50) | 0.53 (0.01 to 19.57) |
| **Zoledronic acid versus placebo** | 0.64 (0.05 to 7.51) | 0.53 (0.04 to 7.06) | 0.72 (0.06 to 8.87) | 0.68 (0.05 to 10.20) | 0.60 (0.05 to 7.80) | 0.65 (0.05 to 8.72) | 0.65 (0.05 to 8.29) |

### 7.3 Summary

No studies were identified comparing denosumab with the primary comparator BSC. One study[29] compared denosumab with zoledronic acid. Another study,[118] comparing zoledronic acid with placebo, contributed data to the indirect comparisons of denosumab versus BSC undertaken by both the Assessment Group and the manufacturer's submission and therefore was also reported in this chapter. In terms of generalisability, both studies were multicentre, international good quality RCTs. The Fizazi study[29] was the larger, randomising 1901 patients compared with 422 for the Saad study.[118] However in the Fizazi study[29] only [redacted] of patients were from the UK. All participants in this study were men aged 18 years or older with life expectancy ≥ 6 months, confirmed prostate cancer and at least one bone metastasis. The exclusion criteria included, amongst others, patients with severe renal impairment or current or previous bisphosphonate treatment for bone metastases, or current or previous ONJ. The study was powered to detect both non-inferiority and superiority with respect to time to first, and time to first-and-subsequent, on-study SRE.

The study by Fizazi and colleagues[29] reported a statistically significant difference in favour of denosumab compared with zoledronic acid in both the median time to first on-study SRE (20.7 versus 17.1 months), most of which were radiation to bone or pathological fractures, and the risk of developing first-and subsequent on-study SREs. The annual skeletal morbidity rate was also significantly lower in the denosumab group, as was the annualised SRE rate.

In the study by Saad and colleagues[118] there was a statistically significant difference in time to first on-study SRE in favour of zoledronic acid compared with placebo (488 versus 321 days), a lower skeletal morbidity rate for the zoledronic acid group and a statistically significant lower incidence in the numbers of patients who experienced at least one SRE in the zoledronic acid group (33.2%) compared with the placebo group (44.2%).

In the denosumab RCT [redacted]. Saad and colleagues[118] did not report this outcome.

In the denosumab study overall survival was similar between the groups (19.4 months for the denosumab group compared with 19.8 for the zoledronic acid group). Saad and colleagues[118] reported a median survival of 546 days (around 18.2 months) for the zoledronic acid group and 464 days (around 15.5 months) for the placebo group.

Denosumab delayed the time to development of moderate or severe pain by around one month compared with zoledronic acid (median 5.8 versus 4.9 months). Saad and colleagues[118] reported that

the mean increase from baseline in pain score at 15 months was 0.58 (95% CI 0.29 to 0.87) for the zoledronic acid group compared with 0.88 (95% CI 0.61 to 1.15) for the placebo group.

In terms of quality of life, for FACT-G, there was a [redacted] Saad and colleagues[118] reported that the total FACT-G score and the EQ-5D scores decreased from baseline to the last measurement, with no statistically significant differences between the zoledronic acid and placebo groups.

In terms of adverse events, there were statistically significantly more hypocalcaemia events in the denosumab group compared with the zoledronic acid group (13% versus 6%), slightly more ONJ events (2% versus 1%) and slightly less adverse events potentially associated with renal impairment (15% versus 16%), while fewer patients in the denosumab group experienced acute phase reactions (8% versus 18%). The rates for adverse events leading to treatment discontinuation, CTCAE grade 3 or 4, serious or fatal adverse events were broadly similar between the denosumab and zoledronic acid groups.

In the study by Saad and colleagues,[118] 2% of patients in the zoledronic acid group experienced grade 3 or 4 hypocalcaemia compared with none in the placebo group and renal function deterioration occurred in 15.2% of patients who received zoledronic acid compared with 11.5% of those receiving placebo (ONJ and acute phase reactions were not reported). Similar proportions of patients who received zoledronic acid (9.8%) and placebo (10.1%) discontinued the study drug because of a serious adverse event.

The AG NMA reported statistically significant differences in favour of denosumab compared with placebo for time to first on-study SRE, risk of developing first-and-subsequent SREs and SMR, [redacted].

# 8 RESULTS - NON-SMALL CELL LUNG CANCER

This chapter reports NSCLC alone. As NSCLC alone, other solid tumours excluding NSCLC and other solid tumours including NSCLC were reported by the same two studies.[30,131] Information on the characteristics of the included studies and quality of the included studies is reported here and not repeated in chapter 9 (Other solid tumours excluding NSCLC) or chapter 10 (Other solid tumours including NSCLC).

## 8.1 Quantity of research available

See chapter 6 section 6.1.

### *8.1.1 Number and type of studies included*

See Section 6.1.1 for the flow diagram outlining the screening process for the overall review.

### *8.1.2 Number and type of studies excluded*

See section 6.1.2 for information on studies that were excluded from the review and Appendix 5 for a list of these studies along with the reasons for their exclusion. These studies were excluded because they failed to meet one or more of the inclusion criteria in terms of types of study, participants, intervention or outcomes reported.

### *8.1.3 Characteristics of the included studies*

Two trials reported on bone metastases secondary to other solid tumours (excluding breast cancer and prostate cancer) and were included for the indirect comparison.[30,131] Both trials included a subgroup of patients with bone metastases secondary to NSCLC and reported outcomes for that group of patients. Appendix 8 shows the characteristics of the included studies. Table 37 shows summary information for the two studies that provided direct evidence for denosumab or were included in the network meta-analysis (NMA).

Data from the trial comparing denosumab with zoledronic acid were derived from three sources; 1) the peer reviewed publication by Henry and colleagues[30] which included multiple myeloma, but also presented certain outcomes for subgroups, 2) the manufacturer's submission, which included a post-hoc analysis excluding 179 patients with multiple myeloma ((n= 800 denosumab, n=797 zoledronic acid included for analysis), and 3) clinical study report 244 including multiple myeloma, which was included with the manufacturer's submission.

**Table 37 Characteristics of the studies included in the network meta-analysis**

| | **Henry 2011**[30] | | **Rosen 2003b**[131] | |
|---|---|---|---|---|
| | **Denosumab** | **ZA** | **ZA** | **Placebo** |
| **Randomised** | 890 | 886 | 257 | 250 |
| **Age, median** | 61 (22-87) | 60 (19-89) | 64 | 64 |
| **Sex- male** | 552 (62%) | 588 (66%) | 158 (61%) | 159 (64%) |
| **ECOG status 1 or less** | 728 (82%) | 748 (84%) | 211 (83%) | 215 (87%) |
| **Primary tumour type** | | | | |
| ***NSCLC*** | 352 (40%) | 350 (39%) | 124 (49%) | 120 (49%) |
| ***Multiple myeloma*** | 93 (10%) | 87 (10%) | NR | NR |
| ***Other*** | 455 (50%) | 449 (51%) | 130 (51%) | 130 (51%) |
| **Time from diagnosis of bone metastasis, months, median (range):** | 2 (0-130) | 2 (0-152) | 3.8 | 2.5 |
| **Previous SREs** | 446 (50%) | 440 (50%) | 166 (65%) | 179 (73%) |

**Notes:**

1. ZA, zoledronic acid; ECOG, Eastern Cooperative Oncology Group.

The study by Henry and colleagues[30] was undertaken between June 2006 and May 2008 and enrolled patients aged 18 years or older with confirmed solid tumours (except breast and prostate) or multiple myeloma and at least one bone metastasis or osteolytic lesion (in the case of multiple myeloma), from 321 centres worldwide. However overall only [redacted] of patients were from the UK.(manufacturer submission) Exclusion criteria included creatinine clearance < 30 mL/min, prior treatment with IV bisphosphonates, planned radiation or surgery to bone, and unhealed dental/oral surgery. Patients received 120 mg denosumab subcutaneously (plus intravenous placebo) or 4 mg zoledronic acid intravenously (adjusted for renal impairment plus subcutaneous placebo) every four weeks. Before the randomisation process, patients were stratified by tumour type that included NSCLC, myeloma, or other; previous SRE and systemic anticancer therapy at enrollment. The overall study was powered to detect non-inferiority and superiority for time to first on-study SRE (primary outcome) and risk of

first-and-subsequent on-study SRE. Study duration was median seven months and length of follow-up was 34 months. The study was funded by Amgen.

The study by Rosen and colleagues[131] enrolled patients aged 18 years or older with osteolytic, osteoblastic, or mixed bone metastases from solid tumours (excluding breast and prostate cancer). Patients received 4 mg or 8 mg zoledronic acid intravenously or placebo every three weeks for nine months. Before the randomisation process, patients were stratified by tumour type that included NSCLC or other solid tumour. The duration of the study was nine months. The primary outcome was the proportion of patients with at least one SRE. During the trial there was a study protocol amendment. Patients randomised to the 8 mg zoledronic acid arm were changed to 4 mg because of renal toxicity concerns.

The study by Henry and colleagues[30] included 40% of patients with NSCLC, 10% with multiple myeloma and 50% with other tumours where half of the included participants belonged to ECOG status 1. Similarly, the study by Rosen and colleagues[131] included 49% of patients with NSCLC and the rest with other solid tumours including SCLC(7-8%), renal cell carcinoma (8-11%), unknown primary (7%), head and neck (2%) thyroid (1-2%) and other (24%) where more than 80% of patients had ECOG status 1 or less.

In the study by Henry and colleagues[30] reporting denosumab, 87% to 96% received antineoplastic or anticancer treatment. However, none of the patients had received previous IV bisphosphonate (BP) treatment. Fifty per cent of the included participants had had a previous SRE at baseline while 40% and 46% had received radiotherapy and surgery respectively. More than 80% had received chemotherapy in the trial by Rosen and colleagues[131] reporting zoledronic acid and 3% had previously received BP treatment, while 68% had had a previous SRE at baseline (65% in ZA and 73% in placebo).

The definition of SRE in both trials included pathological fracture, radiation or surgery to bone, and spinal cord compression. In addition, Rosen and colleagues[131] included hypercalcaemia in the definition of SRE for secondary efficacy analysis. A subsequent SRE was defined as an event occurring more than 21 days after the previous SRE in both trials by Henry and colleagues[30] and Rosen and colleagues.[131]

The characteristics of the subgroup of patients with bone metastases from NSCLC was reported in the manufacturer's clinical study report 244 of the denosumab RCT and are shown in Table 38.

**Table 38 Characteristics of the subgroup of patients with NSCLC (denosumab trial)**

| | Denosumab (n=350) | Zoledronic acid (n=352) |
|---|---|---|
| **Mean age (SD)** | [redacted] | [redacted] |
| **Proportion female** | [redacted] | [redacted] |
| **Time from diagnosis to randomisation, median months (range):** | [redacted] | [redacted] |
| ***Of lung cancer*** | [redacted] | [redacted] |
| ***Of bone metastases*** | [redacted] | [redacted] |
| **Visceral metastases** | [redacted] | [redacted] |
| **ECOG status:** | [redacted] | [redacted] |
| **0** | [redacted] | [redacted] |
| **1** | [redacted] | [redacted] |
| **2** | | |

Source: CSR 244.

### *8.1.4 Quality of the included studies*

Table 39 shows the results of the risk of bias assessment for the studies by Henry and colleagues[30] and Rosen and colleagues.[131]

**Table 39 Results of the risk of bias assessment**

| | Henry 2011[30] | Rosen 2003b[131] |
|---|---|---|
| **Adequate sequence generation** | Yes | Unclear |
| **Adequate allocation concealment** | Yes | Unclear |
| **Blinding** | Yes | Yes |
| **Incomplete outcome data addressed** | Yes | No |
| **Free of selective reporting** | Yes | Yes |

The study by Henry and colleagues[30] was of good quality with low risk of bias as assessed against the criteria in Table 39. In the study by Rosen and colleagues[131] it was unclear whether sequence generation and allocation concealment were adequate. The study by Henry and colleagues[30] used an interactive voice response system to randomly assign patients (1:1 ratio) to treatment groups. An individual independent of the study team prepared the random assignment schedule. The study was double blind and study dose and outcomes were blinded throughout the primary analysis. There was adequate description of withdrawals and losses to follow up and all of the prespecified outcomes were

reported. Both primary and secondary efficacy endpoints included all randomised patients (intention to treat analysis).

The study by Rosen and colleagues[131] did not state the randomisation process and only mentioned that the participants were stratified by tumour type before randomisation. The study was double blind, patients lost to follow-up were described and all of the prespecified outcomes were reported, however not all secondary outcomes were fully reported.

## 8.2 Assessment of effectiveness

### *8.2.1 Time to first on-study SRE*

Henry and colleagues[30] reported a hazard ratio of 0.84 (95% CI 0.64 to 1.10, p=0.20) for denosumab compared with zoledronic acid for time to first on-study SRE for NSCLC, indicating a non-significant risk reduction for denosumab compared with zoledronic acid. [redacted] (CSR244)

The study by Rosen and colleagues[131] reported longer median time to first-on study SRE in the zoledronic acid group compared with the placebo group (171 versus 151 days), however the difference was not significant (p=0.188).

Neither study reported *SRE by type* or *Prior history of SRE* for this outcome.

### *8.2.2 Risk of first-and-subsequent on-study SRE*

The study by Henry and colleagues[30] did not report the risk of developing multiple SREs (first-and-subsequent on-study SREs) for the NSCLC subgroup. [redacted] (CSR 244)

In the study by Rosen and colleagues,[131] a 27% risk reduction of multiple SREs by the use of zoledronic acid was reported relative to placebo (HR 0.73, p= 0.061). A similar risk reduction was reported when HCM was included in the analysis (HR 0.71, p=0.036).

Neither study reported *SRE by type* or *Prior history of SRE* for this outcome.

### *8.2.3 Skeletal morbidity rate*

Neither study reported SMR for the NSCLC subgroup.

### *8.2.4 Incidence of SREs*

[redacted] (CSR 244)

The study by Rosen and colleagues[131] reported that in the NSCLC group of patients, a similar proportion of patients experienced SREs in the zoledronic acid group and in the placebo group (42% versus 45%, p=0.007).

Neither study reported *SRE by type* or *Prior history of SRE* for this outcome.

### *8.2.5 Prevention of hypercalcaemia*

Neither study reported hypercalcaemia for the NSCLC subgroup.

### *8.2.6 Overall survival*

An ad hoc analysis for overall survival in a trial by Henry and colleagues[30] reported that denosumab significantly improved overall survival relative to zoledronic acid by 21% (HR 0.79, 95%CI 0.65 to 0.95).

The study by Rosen and colleagues[131] did not report this outcome.

*Prior history of SRE*

Neither study reported overall survival by prior history of SRE for those with NSCLC.

### *8.2.7 Pain*

Neither study reported this outcome for those with NSCLC.

### *8.2.8 Health related quality of life*

Neither study reported this outcome for those with NSCLC.

### *8.2.9 Adverse events related to treatment*

There were no published or unpublished data on adverse events including hypocalcaemia, osteonecrosis of the jaw, renal toxicity, acute phase reactions or other adverse events reported separately for those with NSCLC. See chapter 10, section 10.2.9 for adverse events reported for all other solid tumours including NSCLC.

### *8.2.10 Network meta-analysis*

The AG group performed a NMA of NSCLC alone, using subgroups from the Henry and Rosen studies.[30,131] The manufacturer did not perform this analysis. Three outcomes were included; time to first on-study SRE (Table 40), risk of first-and-subsequent SRE (Table 41) and the proportion of patients with an on-study SRE (Table 42).

*Time to first on-study SRE*

The results for time to first on-study SRE are shown in Table 40. The NMA results were statistically significant in favour of denosumab compared with zoledronic acid or placebo for time to first on-study SRE.

**Table 40 Time to first on-study SRE**

| | **AG NMA**<br>**HR (95%CI)** |
|---|---|
| **Denosumab versus zoledronic acid** | 0.79 (0.76 to 0.81) |
| **Denosumab versus placebo** | 0.66 (0.63 to 0.68) |
| **Zoledronic acid versus placebo** | 0.86 (0.84 to 0.89) |

*Risk of first-and-subsequent on-study SREs*

The results for the risk of developing time to first-and-subsequent on-study SREs are presented below in Table 41. The NMA results favoured denosumab compared with zoledronic acid or placebo for risk of developing first-and-subsequent SREs, although only the result versus placebo was statistically significant.

**Table 41 Risk of first-and-subsequent SREs**

| | **AG NMA**<br>**RR (95%CI)** |
|---|---|
| **Denosumab versus zoledronic acid** | 0.97 (0.95 to 1.01) |
| **Denosumab versus placebo** | 0.69 (0.66 to 0.73) |
| **Zoledronic acid versus placebo** | 0.73 (0.71 to 0.75) |

*Proportion of patients with on-study SRE*

Results for the proportion of patients with an on-study SRE are shown below in Table 42. The NMA results favoured denosumab compared with zoledronic acid or placebo for the proportion of patients with an on-study SRE but were not statistically significant. These results should be interpreted with

additional caution since this outcome does not differentiate between length of study, thereby adding to the uncertainty.

**Table 42 Proportion of patients with on-study SRE**

| | **AG NMA**<br>**OR (95%CI)** |
|---|---|
| **Denosumab versus zoledronic acid** | 0.96 (0.08 to 11.7) |
| **Denosumab versus placebo** | 0.83 (0.02 to 30.6) |
| **Zoledronic acid versus placebo** | 0.87 (0.07 to 11.2) |

## 8.3 Summary

Only one study, by Henry and colleagues[30] was identified that compared denosumab with zoledronic acid. Another study comparing zoledronic acid with placebo by Rosen and colleagues[131] met the inclusion criteria for the network meta-analysis and thus was reported in this chapter. The study by Henry and colleagues[30] was a good quality RCT with low risk of bias while the study by Rosen and colleagues[131] did not report sufficient information on randomisation. In terms of generalisability, the Henry study[30] was multicentre and international while the Rosen study[131] was multicentre. However in these studies patients with NSCLC did not form the whole patient population but rather were a subgroup of a population that included patients with bone metastases from a range of other solid tumours, excluding breast and prostate cancer. The studies reported outcomes for all other solid tumours grouped together, and separately for NSCLC (approximately 40% (n=702) of patients in the Henry study[30] and 50% (n=244) in the Rosen study[131]) and other solid tumours excluding NSCLC. The proportion of NSCLC patients from the UK was not reported. In both studies the exclusion criteria included, amongst others, patients with severe renal impairment or prior treatment with bisphosphonates. Study duration was longer in the Henry trial[30] (primary analysis at 34 months) compared with the Rosen trial[131] (9 months). The Henry study[30] 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.

For those with bone metastases from NSCLC, a non-significant difference favouring denosumab over zoledronic acid in time to first on-study SRE was reported in the study by Henry and colleagues.[30] [redacted] (CSR 244) No data were reported on skeletal morbidity rate, incidence of SRE, hypercalcaemia, pain or quality of life. The study by Henry and colleagues[30] reported a statistically significant difference in favour of denosumab for overall survival (21% risk reduction with denosumab).

The study by Rosen and colleagues[131] reported a non-significant difference favouring zoledronic acid over placebo in time to first SRE and time to first-and-subsequent SRE. A similar proportion of SREs were reported in the two groups. No data were reported for SMR, hypercalcaemia, overall survival, pain or quality of life. Adverse events were not reported separately for the subgroup of patients with NSCLC.

In the AG NMA, there was a statistically significant difference in favour of densoumab compared with placebo for time to first on-study SRE and risk of developing first-and-subsequent SREs, while the direction of effect for SMR favoured denosumab but was not statistically significant.

# 9 RESULTS - OTHER SOLID TUMOURS (EXCLUDING NSCLC)

This chapter reports outcomes for other solid tumours excluding NSCLC, breast cancer, prostate cancer or multiple myeloma.

## 9.1 Quantity of research available

See chapter 6, section 6.1.

### *9.1.1 Number and type of studies included*

See section 6.1.1 for the flow diagram outlining the screening process for the overall review.

### *9.1.2 Number and type of studies excluded*

See section 6.1.2 for information on studies that were excluded from the review and Appendix 5 for a list of these studies along with the reasons for their exclusion. These studies were excluded because they failed to meet one or more of the inclusion criteria in terms of types of study, participants, interventions or outcomes reported.

### *9.1.3 Characteristics of the included studies*

As these were the same trials that reported the subgroup of patients with lung cancer separately (Henry and Rosen), see section 8.1.3 for details of the characteristics of the included studies for the overall studies.

### *9.1.4 Quality of the included studies*

As these were the same trials that reported the subgroup of patients with lung cancer separately, see section 8.1.4 for details of the quality of the included studies for the overall studies.

## 9.2 Assessment of effectiveness

### *9.2.1 Time to first on-study SRE*

Henry and colleagues[30] reported that denosumab reduced the risk of having a first on-study SRE relative to zoledronic acid by 21% (HR 0.79, 95%CI, 0.62 to 0.99, p=0.04) for other solid tumours excluding NSCLC. The CSR 244 reported median time to first-on study SRE to be [redacted] for zoledronic acid and [redacted] for the denosumab group.

The study by Rosen and colleagues[131] reported a significantly longer median time to developing a first SRE with the use of zoledronic acid (314 days) compared with placebo (168 days) (p=0.051).

Neither study reported *SRE by type* or *prior history of SRE* for this outcome for the subgroup with other solid tumours excluding NSCLC.

### *9.2.2 Risk of first-and-subsequent on-study SRE*

The published paper by Henry and colleagues[30] did not report risk of developing first-and-subsequent on-study SREs. [redacted] (CSR 244)

The study by Rosen and colleagues[131] reported a 26% reduction in the risk of developing multiple SREs for the zoledronic acid group compared with the placebo group (HR 0.74, CI not reported), however the difference was non-significant (p=0.136).

Neither study reported *SRE by type* or *prior history of SRE* for this outcome for the subgroup of patients with other solid tumours excluding NSCLC.

### *9.2.3 Skeletal morbidity rate*

Neither study reported SMR for those with other solid tumours excluding NSCLC.

### *9.2.4 Incidence of SREs*

The published study by Henry and colleagues[30] did not report incidence of SREs for the subgroup of patients with other solid tumours excluding NSCLC. [redacted] (CSR 244)

In the study by Rosen and colleagues,[131] the proportion of patients with an SRE was significantly lower in the zoledronic acid group (33%) compared with the placebo group (43%) (p=0.11) for those with other solid tumours (excluding NSCLC).

Neither study reported *SRE by type* or *prior history of SRE* for this outcome for the subgroup of patients with other solid tumours excluding NSCLC.

### *9.2.5 Prevention of hypercalcaemia*

Neither study reported prevention of hypercalcaemia for those with other solid tumours excluding NSCLC.

9.2.6 Overall survival

*All patients*

An ad hoc analysis by Henry and colleagues[30] reported a non-significant difference in overall survival between the denosumab and zoledronic acid groups (HR 1.08, 95% CI 0.90 to 1.30).

The study by Rosen and colleagues[131] did not report overall survival for those with other solid tumours excluding NSCLC.

*Prior history of SRE*

Neither study reported overall survival by prior history of SRE for those with other solid tumours excluding NSCLC.

### *9.2.7 Pain*

Neither study reported the outcome of pain for those with other solid tumours excluding NSCLC.

### *9.2.8 Health related quality of life*

Neither study reported quality of life for those with other solid tumours excluding NSCLC.

### *9.2.9 Adverse events related to treatment*

Adverse events including hypocalcaemia, osteonecrosis of the jaw, renal toxicity, acute phase reactions or other adverse events were not reported separately for those with other solid tumours excluding NSCLC. See chapter 10, section 10.2.9 for information on adverse events reported for patients with other solid tumours including NSCLC.

### *9.2.10 Network meta-analysis*

The assessment group (AG) group performed a NMA of other solid tumours (OST), excluding breast, prostate, multiple myeloma and NSCLC, using subgroups from the Henry and Rosen studies.[30,131] The manufacturer did not perform this analysis. Three outcomes were included: time to first on-study SRE (Table 43), risk of first-and-subsequent on-study SRE (Table 44) and the proportion of patients with an on-study SRE (Table 45).

*Time to first on-study SRE*

The results for time to first on-study SRE are shown in Table 43. There was a statistically significant difference in favour of denosumab compared with zoledronic acid or placebo for this outcome.

**Table 43 Time to first on-study SRE**

| | **AG NMA**<br>**HR (95%CI)** |
|---|---|
| **Denosumab versus zoledronic acid** | 0.93 (0.89 to 0.96) |
| **Denosumab versus placebo** | 0.37 (0.35 to 0.39) |
| **Zoledronic acid versus placebo** | 0.42 (0.40 to 0.44) |

*Risk of first-and-subsequent on-study SRE*

The NMA results for risk of developing first-and-subsequent SREs are presented in Table 44. There was a statistically significant difference in favour of denosumab compared with zoledronic acid or placebo for this outcome.

**Table 44 Risk of first-and-subsequent SREs**

| | **AG NMA**<br>**RR (95%CI)** |
|---|---|
| **Denosumab versus zoledronic acid** | 0.82 (0.79 to 0.84) |
| **Denosumab versus placebo** | 0.67 (0.64 to 0.70) |
| **Zoledronic acid versus placebo** | 0.81 (0.79 to 0.83) |

*Proportion of patients with on study SRE*

The results for the proportion of patients with an on-study SRE are shown in Table 45. The results for denosumab compared with zoledronic acid or placebo were not statistically significant although the direction of effect favoured denosumab. These results should be interpreted with additional caution since this outcome does not differentiate between length of study, thereby adding to the uncertainty.

**Table 45 Proportion of patients with an on-study SRE**

| | **AG NMA**<br>**OR (95%CI)** |
|---|---|
| **Denosumab versus zoledronic acid** | 0.68 (0.05 to 8.81) |
| **Denosumab versus placebo** | 0.44 (0.01 to 17.13) |
| **Zoledronic acid versus placebo** | 0.65 (0.05 to 8.19) |

## 9.3 Summary

As these two studies were the same studies that contained the subgroups of NSCLC patients, see also section 8.3 for information on the characteristics, quality and generalisability of the overall studies. One further point to note in terms of generalisability is that data from patients with a range of

different types of solid tumour (excluding breast, prostate or NSCLC) were pooled to provide an overall estimate for other solid tumours. The Henry study[30] was not powered to detect non-inferiority or superiority for other solid tumours excluding NSCLC.

For those with bone metastases from other solid tumours excluding NSCLC, there was a significant risk reduction for denosumab compared with zoledronic acid in time to first on-study SRE (21% reduction with denosumab in the study by Henry and colleagues[30]) but [redacted].(CSR 244) [redacted]. In the study by Henry and colleagues[30] (2011), no statistical significant difference was reported for overall survival. No data were reported for SMR, hypercalcaemia, pain or quality of life.

The study by Rosen and colleagues[131] reported a statistically significant difference between zoledronic acid and placebo in time to first on-study SRE (314 days vs 168 days); however, a non significant difference in risk of first-and-subsequent on-study SREs was reported. Significantly lower incidence of SREs was reported for zoledronic acid (33%) compared with placebo (43%), however the difference was not statistically significant (p=0.11). No data were reported for hypercalcaemia, overall survival, pain or quality of life. Adverse events were not reported separately for other solid tumours excluding NSCLC.

In the AG NMA, there was a statistically significant difference in favour of denosumab compared with placebo for time to first on-study SRE and risk of developing first-and-subsequent SREs, while for the proportion of patients with an on-study SRE there was no statistically significant difference, although the direction of effect favoured denosumab.

# 10 RESULTS – OTHER SOLID TUMOURS (INCLUDING NSCLC)

This chapter reports outcomes for other solid tumours including NSCLC (but excluding breast cancer or prostate cancer). Data taken from the clinical study report (CSR) may include multiple myeloma and this has been highlighted where applicable.

## 10.1 Quantity of research available

See chapter 6, section 6.1

### *10.1.1 Number and type of studies included*

See section 6.1.1 for the flow diagram outlining the screening process for the overall review.

### *10.1.2 Number and type of studies excluded*

See section 6.1.2 for information on studies that were excluded from the review and Appendix 5 for a list of these studies along with the reasons for their exclusion. These studies were excluded because they failed to meet one or more of the inclusion criteria in terms of types of study, participants, intervention or outcomes reported.

### *10.1.3 Characteristics of the included studies*

As these were the same trials (Henry and Rosen) that reported the subgroup of patients with lung cancer separately, see section 8.1.3 for details of the characteristics of the included studies.

### *10.1.4 Quality of the included studies*

As these were the same trials that reported the subgroup of patients with lung cancer separately, see section 8.1.4 for details of the quality of the included studies.

## 10.2 Assessment of effectiveness

### *10.2.1 Time to first on-study SRE*

Results on time to first on-study SRE are shown in Table 46. In the manufacturer's submission, post hoc analysis of study 244 of other solid tumours (excluding myeloma), the median time to first on-study SRE was longer for denosumab ([redacted]) compared with zoledronic acid ([redacted]) with a risk reduction of 19% ([redacted]). [redacted] of patients in the zoledronic acid group and [redacted] in the denosumab group were reported to experience a first on-study SRE. The manufacturer's submission (excluding multiple myeloma) further reported that the median time to first symptomatic SRE was [redacted] for zoledronic acid and was [redacted] for denosumab, with risk reduction of [redacted]

The study by Henry and colleagues[30] (including multiple myeloma) reported a statistically significant difference in favour of denosuamb compared with zoledronic acid in delaying time to first on-study SRE by 16% (HR 0.84, 95%CI, 0.71 to 0.98, p=0.0007). The median time to first on-study SRE was significantly longer for denosumab (20.6 months) than for zoledronic acid (16.3 months) (p=0.03). However, when adjusted for multiple comparisons (using the Hochberg procedure) to test for superiority for time to first SRE, the difference was not significant (p=0.06).

The study by Rosen and colleagues[131] reported significantly longer median time to first SRE for zoledronic acid (230 days) compared with placebo (163 days) (p=0.023). Analysis of median time to first event excluding HCM and including death was longer for zoledronic acid (136 days) compared with placebo (93 days) (p=0.039).

**Table 46 Time to first on-study SRE**

| Study ID | Measures | Denosumab | Zoledronic acid | P value |
|---|---|---|---|---|
| Henry 2011[30] (including multiple myeloma) | Number randomised | 890 | 886 | NA |
| | Median months | 20.6 | 16.3 | 0.03 |
| | HR (95%CI) | 0.84 (0.71 to 0.98) | | 0.0007 |
| Post hoc analysis CSR 244 (excluding multiple myeloma) | Number randomised | 800 | 797 | NA |
| | Median months | [redacted] | [redacted] | NA |
| | HR (95%CI) | [redacted] | | [redacted] |

NA: not applicable

Source: Henry 2011[30] and manufacturer submission

*SRE by type*

The time to radiation to the bone was reported in the post-hoc analysis of study 244 (excluding multiple myeloma). The median time to radiation to the bone was [redacted] in the zoledronic group but was [redacted] in the denosumab group, with a risk reduction of [redacted] for denosumab [redacted]. (manufacturer submission)

In the study by Henry and colleagues[30] (including multiple myeloma), denosumab reduced the risk of having radiation to bone by 22% compared with zoledronic acid (HR=0.78 95% CI: 0.63, 0.97 (p=0.03)).[135]

[redacted] (CSR 244)

Table 47 shows the distribution of first on-study SRE by type of SRE as reported in the manufacturer's submission (post hoc analysis of CSR 244, excluding multiple myeloma). The distribution of type of SRE was similar across the treatment groups, with radiation to bone and pathological fracture being the most commonly occurring.

**Table 47 Patients with first on-study SRE by type (post hoc analysis of CSR 244)**

| | **Denosumab (n=800 randomised)** | **Zoledronic acid (n=797 randomised)** |
|---|---|---|
| | **Number of events (%)** | **Number of events (%)** |
| **Overall** | [redacted] | [redacted] |
| **Radiation to bone** | [redacted] | [redacted] |
| **Pathological fracture** | [redacted] | [redacted] |
| **Spinal cord compression** | [redacted] | [redacted] |
| **Surgery to bone** | [redacted] | [redacted] |

Source: manufacturer submission.

The study by Rosen and colleagues[131] reported that the median time was not reached for individual SRE except for median time to first pathological fracture which was longer in the zoledronic acid group (238 days) compared with the placebo group (161 days) (p=0.031). Rosen and colleagues[131] further reported that the time to first vertebral fracture and time to first radiation therapy were significantly longer in the zoledronic acid group (p=0.05).

*Prior history of SRE*

The manufacturer's submission reported time to first on-study SRE by prior history of SRE for post hoc study 244 (excluding myeloma) (Table 48). [redacted]

[redacted]

**Table 48 Subgroup analysis by prior SRE history for time to first-on study SRE (post hoc analysis of CSR 244), excluding multiple myeloma**

| | | Denosumab | Zoledronic acid |
|---|---|---|---|
| **Overall** | **Number** | 800 | 797 |
| | **HR (95% CI)** | [redacted] | |
| | **p-value** | [redacted] | |
| **No prior SRE** | **Number** | [redacted] | [redacted] |
| | **HR (95% CI)** | [redacted] | |
| | **p-value** | [redacted] | |
| **Prior SRE** | **Number** | [redacted] | [redacted] |
| | **HR (95% CI)** | [redacted] | |
| | **p-value** | [redacted] | |
| **Covariate effect** | **Pt estimate (95% CI)** | [redacted] | |
| | **P value** | [redacted] | |

Source: manufacturer submission.

The published study by Henry and colleagues[30] did not report time to first on-study SRE by previous history of SRE. [redacted] (CSR 244)

Rosen and colleagues[131] did not report time to first-on study SRE by previous history of SRE.

### *10.2.2 Risk of first-and-subsequent on-study SREs*

The manufacturer's submission (post hoc analysis of study 244 excluding multiple myeloma) reported that denosumab reduced the risk of developing first-and-subsequent SREs compared with zoledronic acid. Using Anderson-Gill multiple event analysis (any events occurring at least 21 days apart), the result demonstrated borderline statistical significance (RR 0.85 95%CI 0.72 to 1.00) (Table 49). The cumulative number of on-study SREs was lower for denosumab (328) than for zoledronic acid (374).(manufacturer submission)

Henry and colleagues[30] (including multiple myeloma) reported a non-significant risk reduction for first-and-subsequent on-study SREs (without the 21-day window) for denosumab compared with zoledronic acid (RR 0.90, 95% CI 0.77 to 1.04, p=0.14).

The study by Rosen and colleagues[131] reported that zoledronic acid reduced the risk of multiple SREs by 27% compared with placebo (HR 0.732, p=0.017).

**Table 49 Risk of first-and-subsequent on-study SRE**

| Study ID | Measures | Denosumab (n=890) | Zoledronic acid (n=886) | P value |
|---|---|---|---|---|
| Henry 2011[30] (including multiple myeloma) | Number randomised | 890 | 886 | NA |
| | Number of events | 392 | 436 | NA |
| | Rate ratio (95%CI) | 0.90 (0.77 to 1.04) | | 0.14 |
| Post hoc analysis CSR 244 (excluding multiple myeloma) | Number analysed | 800 | 797 | NA |
| | Number of events | 328 | 374 | NA |
| | Rate ratio (95%CI) | 0.85 (0.72 to 1.00) | | 0.048 |

NA: not applicable

Source: Henry 2011[30] and manufacturer submission.

*SRE by type*

Neither study reported multiple event analysis for SRE by type.

In the manufacturer's submission (post hoc analysis CSR 244), there was no difference reported between denosumab and zoledronic acid for the proportion of patients with each type of SRE. The distribution of each type of SRE is shown in Table 50. Radiation to bone and pathological fracture were the most commonly occurring SREs while surgery to bone and spinal cord compression were reported for only a small proportion of patients.

The published studies by Henry and colleagues[30] and Rosen and colleagues[131] did not report on risk of first-and-subsequent on-study SREs by type of SRE.

**Table 50 Patients with first-and-subsequent on-study SRE by type (post hoc analysis of CSR 244)**

| | Denosumab (n=800 randomised) | Zoledronic acid (n=797 randomised) |
|---|---|---|
| | Number of events (%) | Number of events (%) |
| **Total number of events** | [redacted] | [redacted] |
| **Radiation to bone** | [redacted] | [redacted] |
| **Pathological fracture** | [redacted] | [redacted] |
| **Spinal cord compression** | [redacted] | [redacted] |
| **Surgery to bone** | [redacted] | [redacted] |

Source: manufacturer submission.

*Prior history of SRE*

The manufacturer's submission reported risk of first-and-subsequent on-study SREs by prior history of SRE for post hoc study 244 (excluding multiple myeloma) (Table 51). [redacted].(manufacturer submission)

[redacted](CSR 244)

The studies by Henry and colleagues[30] and Rosen and colleagues[131] did not report risk of first-and-subsequent on-study SREs by prior history of SRE.

**Table 51 Risk of first-and-subsequent on-study SREs by prior history of SRE**

| | | Denosumab | Zoledronic acid |
|---|---|---|---|
| **Overall** | **Number** | 800 | 797 |
| | **HR (95% CI)** | | |
| | **p-value** | | |
| **No prior SRE** | **Number** | | |
| | **HR (95% CI)** | | |
| | **p-value** | | |
| **Prior SRE** | **Number** | | |
| | **HR (95% CI)** | | |
| | **p-value** | | |
| **Covariate effect** | **Pt estimate (95% CI)** | | |
| | **P value** | | |

Source: manufacturer submission

### *10.2.3 Skeletal morbidity rate*

The published study by Henry and colleagues[30] did not report data on SMR.

(Table 52).

(CSR 244)

The study by Rosen and colleagues[131] reported slightly lower SMR (the number of events per year) for zoledronic acid (2.24 [SD 9.12]) compared with placebo (2.52 [SD 5.11]), however the difference was non-significant (p=0.069). Statistically significant lower SMR was reported for zoledronic acid compared with placebo when hypercalcaemia was included in the analysis (2.24 [SD 9.12] vs 2.73 [SD 5.29]).

*SRE by type*

SMR by type of SRE was not reported for the denosumab RCT.

*The study by Rosen and colleagues[131] stated that the skeletal morbidity rate for each type of SRE was lower in the zoledronic acid treatment groups compared with the placebo group except for surgery to bone and spinal cord compression; however no data were reported.*

*Prior history of SRE*

Neither study reported SMR by prior history of SRE.

### *10.2.4 Incidence of SREs*

The study by Henry and colleagues[30] did not report incidence of SREs. In the manufacturer submission (post hoc analysis of CSR 244 excluding multiple myeloma), the annualised SRE rate (number of events per subject years) [redacted] The results are shown in Table 52.

[redacted] (CSR 244)

The study by Rosen and colleagues[131] reported a non-significant difference between zoledronic acid and placebo in the proportion of SREs experienced (38% vs 44%, p=0.127).

**Table 52 Annualised SRE rate and skeletal morbidity rate in post hoc study CSR 244**

| | Denosumab (n=800) | Zoledronic acid (n=797) |
|---|---|---|
| **Annualised SRE rate per patient** | | |
| Subject years | [redacted] | [redacted] |
| **Without 21-day window** | | |
| Number of events | [redacted] | [redacted] |
| Annualised rate | [redacted] | [redacted] |
| **Without 21-day window** | | |
| Number of events | [redacted] | [redacted] |
| Annualised rate | [redacted] | [redacted] |
| **Mean annual SMR** | | |
| Rate | [redacted] | [redacted] |
| p-value | [redacted] | |

Source: manufacturer submission.

*SRE by type*

Incidence of SREs by SRE type was not reported for the denosumab RCT.

Rosen and colleagues[131] reported the distribution of SRE type in zoledronic acid compared with placebo as shown in Table 53. For each individual SRE, a lower proportion of patients receiving zoledronic acid experienced an SRE than those receiving placebo. Radiation to bone and pathological fracture were the most frequently occurring SREs while spinal cord compression occurred least.

**Table 53 Proportion of patients experiencing SRE by type**

| | Zoledronic acid (n=257 randomised) | Placebo (n=250 randomised) | P value |
|---|---|---|---|
| | **Number of events (%)** | **Number of events (%)** | |
| **All SRE (excluding HCM)** | 38% | 44% | 0.127 |
| **Radiation to bone** | 69 (27%) | 81 (32%) | NR |
| **Pathological fracture**<br>***Vertebral***<br>***Nonvertebral*** | 40 (16%)<br>20 (8%)<br>26 (10%) | 53 (21%)<br>30 (12%)<br>29 (12%) | NR |
| **Surgery to bone** | 11 (4%) | 9 (4%) | NR |
| **Spinal cord compression** | 7 (3%) | 10 (4%) | NR |
| **Hypercalcaemia of malignancy** | 0 | 8 (3%) | 0.004 |
| **Any SRE (including HCM)** | 97 (38%) | 117 (47%) | 0.039 |

NR: not reported

Source: Rosen 2003b[131]

*Prior history of SRE*

Neither study reported incidence of SRE by prior history of SRE.

### *10.2.5 Prevention of hypercalcaemia*

[redacted] (CSR 244)

In the study by Rosen and colleagues[131] there was no HCM in the zoledronic group while in the placebo group 3% of patients experienced HCM.

### *10.2.6 Overall survival*

Henry and colleagues[30] reported no difference between denosumab and zoledronic acid for overall survival (HR 0.95, 95%CI 0.83 to 1.08, p=0.43). In the manufacturer's submission median overall survival was balanced between the groups, with median time for survival [redacted] months in the denosumab group and [redacted] months in the zoledronic acid group. The risk reduction for overall survival was not statistically significant (0.92, 95% CI 0.81 to 1.05, p=0.2149).

Rosen and colleagues[131] reported time to median death which was similar in the zoledronic acid group (203 days) and the placebo group (183 days) (p=0.623).

*Prior history of SRE*

Neither study reported overall survival by prior history of SRE.

### *10.2.7 Pain*

The manufacturer's submission reported pain outcomes assessed using BPI-SF. The median time to developing moderate or severe worst pain was evaluated in a subgroup of patients with no/mild pain ( for denosumab; for zoledronic acid). The median time to developing moderate or severe worst pain (worst pain score >4) in this group was longer in the denosumab group ( ) than in the zoledronic acid group ( ) with a risk reduction in the denosumab group ( ). The manufacturer's submission further reported that denosumab delayed the time to worsening pain (>=2 point increase from baseline in BPI-SF worst pain score) compared with zoledronic acid (4.7 months versus 3.9 months, p=0.040) ( ). The study by Henry and colleagues[135] reported similar results in those with other solid tumours and including multiple myeloma (169 days vs 143 days; HR 0.85, 95%CI 0.73 to 0.98, p=0.02).

(CSR 244)

There was no statistically significant difference at study end point in the use of strong analgesics in OST (post hoc analysis excluding multiple myeloma).

(manufacturer submission)

(CSR 244)

The study by Rosen and colleagues[131] comparing zoledronic acid with placebo reported an increase in pain score from baseline to month 9 for mean BPI composite pain score and mean analgesic score in both groups, suggesting increased pain and use of analgesics. This study further reported that the

mean composite pain score was decreased from baseline to month 9 for zoledronic acid for those who had pain at baseline; however no data were reported.

### *10.2.8 Health related quality of life*

*FACT-G*

[redacted] (Table 54).(manufacturer submission)

[redacted] (CSR 244)

The study by Rosen and colleagues[131] stated that there were no statistically significant differences between zoledronic acid and placebo with respect to any of these global quality-of-life outcomes and that changes in FACT-G scores were also comparable between treatment groups; however, no data were reported.

**Table 54 Change in FACT scores from baseline to week 45 in post hoc study CSR 244**

| | Dmab 120 mg N=800 | | ZA 4 mg N=797 | |
|---|---|---|---|---|
| | Baseline Mean (SD) | Change from baseline to Wk 45 Mean (SD) | Baseline Mean (SD) | Change from baseline to Wk 45 Mean (SD) |
| Physical wellbeing | [redacted] | [redacted] | [redacted] | [redacted] |
| Functional wellbeing | [redacted] | [redacted] | [redacted] | [redacted] |
| FACT-G total score | [redacted] | [redacted] | [redacted] | [redacted] |

Source: manufacturer submission.

EQ-5D

[redacted] (CSR 244)

### *10.2.9 Adverse events related to treatment*

*Hypocalcaemia*

Henry and colleagues[30] reported that 10% of denosumab treated patients had hypocalcaemia compared with 5.8% of zoledronic acid treated patients. The statistical difference between the groups was not reported. The manufacturer's submission reported that [redacted] of denosumab treated patients and [redacted] of zoledronic acid treated patients reported serious hypocalcaemia events. Although the number of patients reporting hypocalcaemia is small the total number of events is higher for denosumab compared with zoledronic acid [redacted] .(CSR 244)

The study by Rosen and colleagues[131] did not report hypocalcaemia.

Observational studies reported a higher incidence of hypocalcaemia compared with the RCTs. However the observational studies are likely to have a broader criteria for hypocalcaemia. Chennuru and colleagues[139] reported an incidence of 8.3% over 2 years in patients prescribed zoledronic acid. Zuradelli and colleagues[162] reported an incidence of 4.6% in patients prescribed zoledronic acid (time at risk not reported).

*Osteonecrosis of the jaw (ONJ)*

Henry and colleagues[30] reported that rates of ONJ were similar in the denosumab (1.3%) and zoledronic acid (1.1%) groups (p=1.00). The cumulative incidence rates of ONJ at years 1 and 3 was reported to be slightly higher in the zoledronic acid group compared with the denosumab group, which was 0.6% versus 0.5% at year 1 and 1.3% versus 1.1% at year 3 (p=1.0). At year 2, ONJ events were slightly higher in the denosumab group (1.1%) compared with the zoledronic acid group (0.9%).

The study by Rosen and colleagues[131] did not report ONJ.

Two large observational studies were found. Hoff and colleagues[148] reported an incidence of 0.7% (29/3994) over 21.2 months in patients taking zoledronic acid or pamidronate. Vahtsevanos and

colleagues[160] reported an incidence of 4.9% (80/1621) over 20.4 months in patients taking any bisphosphonate.

*Renal toxicity*

Henry and colleagues[30] reported that renal adverse events occurred more often in the zoledronic acid group (10.9%) than in the denosumab group (8.3%). In both treatment groups, renal failure was reported to be similar. The manufacturer's submission reported a higher number of patients in the zoledronic acid group compared with the denosumab group (34 patients compared with 24 patients). [redacted].(CSR 244) The small discrepancy in these results is unclear.

The study by Rosen and colleagues[131] reported that the proportion of patients with decreased renal function was higher in the zoledronic acid group than in the placebo group. When zoledronic acid was given as a 5 minute infusion, the proportion of patients with decreased renal function was much higher in the zoledronic acid group (16.4%) than in the placebo group (5.6%). After the implementation of a 15 minute infusion of the given dose, 10.9% in the zoledronic acid group and 6.7% in the placebo group experienced decreased renal function.

The largest observational study[156] (n=966) evaluated renal impairment in patients taking any bisphosphonate and found an incidence of 2.9% over 9.6 months.

*Acute phase reactions*

Henry and colleagues[30] reported that acute phase reactions occurred more often in the zoledronic acid group (14.5%) than in the denosumab group (6.9%). In the manufacturer submission, serious adverse events of acute phase reaction within three days of first dose [redacted]

Rosen and colleagues did not report this outcome.[131]

*Other adverse events*

In the study by Henry and colleagues,[30] serious adverse events were reported in 66% of those treated with zoledronic acid and in 63% of those treated with denosumab (p=0.16). Pyrexia and anaemia were reported to be significantly higher in the zoledronic acid group compared with the denosumab group. Other adverse events were similar in both groups.

In the study by Rosen and colleagues,[131] a higher proportion in the zoledronic acid group compared with the placebo group was reported to have nausea (46% vs 34%), vomiting (36% vs 29%) and

dyspnoea (33% vs 26%). The event of bone pain was reported to be higher in the placebo group (59%) than in the zoledronic acid group (51%).

There were no other adverse events of note from the observational studies assessed. Anaemia was similar between all groups.

For details of all other adverse extracted from the RCTs meeting the review's inclusion criteria and also adverse events extracted from a number of observational studies identified, see Appendix 12.

### *10.2.10 Network meta-analysis*

The assessment group (AG) and manufacturer performed a network meta-analysis (NMA) of other solid tumours excluding breast and prostate but including NSCLC. Two studies were included in each NMA (Henry and Rosen). Including a mixture of cancers within a NMA increases heterogeneity significantly. Therefore these results should be interpreted with caution. The AG also performed a NMA of the proportion of patients with an on-study SRE.

*Time to first on-study SRE*

The results for time to first on-study SRE are shown in Table 55. The AG NMA results were statistically significant in favour of denosumab compared with zoledronic acid or placebo, [redacted].

**Table 55 Time to first on-study SRE**

| | **AG NMA HR (95%CI)** | **MS NMA HR (95%CI)** |
|---|---|---|
| **Denosumab versus zoledronic acid** | 0.93 (0.90 to 0.96) | [redacted] |
| **Denosumab versus placebo** | 0.44 (0.42 to 0.46) | [redacted] |
| **Zoledronic acid versus placebo** | 0.53 (0.51 to 0.54) | [redacted] |

*Risk of first-and-subsequent on-study SREs*

The results for risk of developing first-and-subsequent on-study SREs are presented in Table 56. The AG NMA results were statistically significant in favour of denosumab compared with zoledronic acid or placebo.

[redacted]

**Table 56 Risk of first-and-subsequent on-study SREs**

| | AG NMA<br>RR (95%CI) | MS NMA<br>HR (95%CI) |
|---|---|---|
| **Denosumab versus zoledronic acid** | 0.87 (0.85 to 0.89) | [redacted] |
| **Denosumab versus placebo** | 0.63 (0.61 to 0.66) | [redacted] |
| **Zoledronic acid versus placebo** | 0.75 (0.74 to 0.77) | [redacted] |

*Proportion of patients with on-study SRE*

The results for the proportion of patients with an on-study SRE are shown in Table 57.

**Table 57 Proportion of patients with on-study SRE**

| | AG NMA<br>OR (95%CI) |
|---|---|
| **Denosumab versus zoledronic acid** | 0.79 (0.07 to 9.45) |
| **Denosumab versus placebo** | 0.58 (0.02 to 19.48) |
| **Zoledronic acid versus placebo** | 0.74 (0.06 to 8.83) |

In the AG NMA, the differences between denosumab and zoledronic acid or placebo were not statistically significant, although the direction of effect favoured denosumab. This outcome does not account for differences in length of study, thereby adding to the uncertainty and therefore these results should be interpreted with caution.

### 10.3 Summary

See also section 8.3, first paragraph for information on the characteristics, quality and generalisability of the studies. In terms of generalisability data from patients with a range of different types of solid tumour (excluding breast or prostate) were pooled to provide an overall estimate for other solid tumours. The Henry study[30] was powered to detect non-inferiority or superiority for other solid tumours including NSCLC and multiple myeloma.

For those with bone metastases from other solid tumours, the study by Henry and colleagues[30] reported a statistically significant difference in favour of denosumab compared with zoledronic acid in delaying time to first on-study SRE (20.6 months vs 16.3 months with 16% risk reduction by denosumab). However, a non-significant difference was reported in the risk of developing first-and-subsequent on-study SREs. The skeletal morbidity rate and annualised SRE rate were also significantly lower in the denosumab group in the study by Henry and colleagues.[30]

The manufacturer's submission reported [redacted] and in risk reduction for first-and-subsequent on-study SRE (15% reduction for denosumab). [redacted] (manufacturer submission) Overall survival was similar for both groups.

In the study by Rosen and colleagues[131] a statistically significant difference in favour of zoledronic acid compared with placebo was reported in time to first SRE (230 days vs 163 days) and risk of developing first-and-subsequent SREs (risk reduction by 27% with zoledronic acid ). No significant difference between the groups was reported for skeletal morbidity rate and for incidence of SRE.

The manufacturer's submission reported a [redacted] In the study by Henry and colleagues[30] no significant difference between denosumab and zoledronic acid in overall survival was reported. Delay in worsening clinically significant pain at 45 weeks was reported which favoured denosumab (169 days) compared with zoledronic acid (143 days). The manufacturer's submission reported that a [redacted]

In the study by Rosen and colleagues[131] no hypercalcaemia events were reported in the zoledronic acid group compared with placebo (3%). No significant differences were reported for overall survival and quality of life (changes in FACT-G scores). No data were reported for pain outcomes.

In the study by Henry and colleagues[30] there were more hypocalcaemia events in the denosumab group (10%) compared to the zoledronic acid group (5.8%), less renal adverse events (8.3% versus 10.9%) and acute phase reactions (6.9% versus 14.5%) while similar events of osteonecrosis of jaw (1.3% versus 1.1%) experienced by patients. The incidence of serious adverse events was similar in both groups (63% vs 66%, p=0.16).

Rosen and colleagues[131] reported that more patients in the zoledronic acid group (10.9%) had decreased renal function compared with placebo (6.7%) and less bone pain (51% versus 59%). No data were reported on hypocalcaemia, osteonecrosis of the jaw or acute phase reaction.

The AG NMA reported a statistically significant difference in favour of denosumab compared with placebo for time to first on-study SRE and risk of developing first-and-subsequent on-study SREs, [redacted].

# 11 ASSESSMENT DESIGN AND RESULTS – COST-EFFECTIVENESS

This chapter consists of the following main sections: 11.1 Systematic reviews of cost-effectiveness studies and quality of life studies; 11.2 Critique of the manufacturer's submission; 11.3 Independent economic assessment.

All costs and prices in this report are in 2010 sterling. Costs in foreign currency amounts are converted to sterling at the April 5th exchange rate of the relevant year. Where no year is stated for prices, it is assumed to be the year of the publication. Indexation to 2010 prices applies the HSCS index as drawn from the PSSRU Unit Costs of Health and Social Care.[168] Original amounts are given in square brackets.

## 11.1 Systematic reviews of cost-effectiveness studies and quality of life studies

### *11.1.1 Search strategy and quantity of research available*

Two separate literatures searches were conducted to identify studies considering cost-effectiveness and quality of life. Firstly, studies focusing on cost-effectiveness or quality of life in relation to bone metastases and SREs were sought; this search identified 468 papers. After having screened the titles and abstracts, 131 full text papers were retrieved.

A second search was conducted to identify studies considering cost-effectiveness or quality of life in relation to denosumab and bisphosphonates. This search identified 2600 papers. After having screened the titles and abstracts, 139 full text papers were retrieved.

The databases searched were: MEDLINE (1948 to May Week 3 2011); Embase (1980 to 2011 Week 21); MEDLINE In-Process & Other Non-Indexed Citations June 02, 2011; NHS Economic Evaluation Database (June 2011); Science Citation Index (1970 - June 2011); Social Science Citation Index (1970 - June 2011); Conference Proceedings Citation Index – Science (1990 – June 2011); Conference Proceedings Citation Index – Social Science & Humanities (1990 – June 2011). Conference proceedings from the 2010 and 2011 meetings of the American Society of Clinical Oncology were handsearched. The searches had no date restrictions but were limited to English language papers.

Full details of the search strategies used and websites consulted are documented in Appendix 1.

### *11.1.2 Results - cost-effectiveness studies*

*Full papers*

Dranitsaris and Hsu[169] estimate the cost effectiveness of pamidronate compared to BSC over a 12 month trial among breast cancer patients with bone metastases. This drew on Hortobagyi and colleagues[22] who report the clinical effectiveness of the then only relevant pamidronate trial. Over the mean duration of therapy of 10 months pamidronate and BSC saw respective rates of:

- 20% vs 30% for non-vertebral fractures
- 19% vs 33% for radiation to the bone
- 4% vs 10% for surgery to the bone
- 46% vs 62% for any SRE
- 43% vs 56% for any SRE excluding hypercalcaemia

Costs per health state were estimated by chart review, with unit costs being drawn from the Princess Margaret Hospital and the Centenary Hospital of Ontario, Canada.

The main aspect of the paper that is of interest is the utility data, which is drawn from a time trade off exercise among 25 women from the Canadian general public and 25 female health workers. There is a lack of detail within the paper, and it seems likely that the health state descriptors include elements of both the treatment aspects and clinical effectiveness for each arm. But with this noted, the TTO exercise yields the following estimates.

**Table 58 Dranitsaris[169] TTO exercise results - healthy months equivalent to one year with pamidronate/placebo with or without SREs**

| | Average public | % | Average heath workers | % |
|---|---|---|---|---|
| **SRE with pamidronate** | 5.46 months | 46% | 4.80 months | 40% |
| **No SRE with pamidronate** | 7.73 months | 64% | 9.92 months | 83% |
| **SRE with placebo** | 3.68 months | 31% | 4.13 months | 34% |
| **No SRE with placebo** | 6.76 months | 56% | 7.89 months | 66% |

The source of the anticipated benefit from pamidronate over placebo when no SRE is experienced is unclear and is not specified within the paper. Health worker responses are reasonably consistent, with a consistent reduction in quality of life from an SRE of around 50% for both the pamidronate and the placebo health states. Results are more mixed within the public responses, with SREs in the placebo group causing a similar approximate 50% reduction in quality of life, but only a 30% reduction in the pamidronate group.

Dranitsaris and Hsu[169] estimate that pamidronate results in an additional cost of £1,758 [CND$2,800]. Based upon the SRE rates including hypercalcaemia of 46% and 62% this results in an estimated gain from pamidronate of 0.15 QALYs, with an associated cost effectiveness of £11,740 [CND$18,700] per QALY based upon public preferences and £10,359 [CND$16,500] per QALY based upon health care worker preferences. Results are sensitive to the costs of surgery to the bone.

Hillner and colleagues[170] estimate the cost effectiveness of pamidronate compared to BSC for breast cancer patients over a two year time horizon in the USA. The utility values are taken from expert opinion, with fractures at 0.8, radiation at 0.6, surgery at 0.4 and both hypercalcaemia and spinal cord compression at 0.2. The duration applied to these is not clear from the paper, but it may be one month. Pamidronate is estimated to result in an additional 1.13 months SRE free with a net cost increase of £3,593 [US$3,968] for chemotherapy patients, resulting in a cost effectiveness of £97,973 [US$108,200] per QALY. For hormonal treated patients the respective amounts are 0.82 additional months free of SRE at a cost of £6,958 [US$7,685] to yield a cost effectiveness of £276,444 [US$305,300] per QALY.

Ross and colleagues,[55] in the 2004 HTA monograph reviewing the role of bisphosphonates in metastatic disease, model the cost per SRE avoided for breast cancer patients with bone metastases. This uses a cost effectiveness markov model with a monthly cycle. This simulates rates of SREs, with the health states also including hypercalcaemia and pain reduction, this latter being distinct from palliative radiotherapy. Note that spinal cord compression is not considered. The relative risks for SREs and hypercalcaemia in the model for bisphosphonates compared to BSC are not differentiated by bisphosphonate, but are differentiated by event type:

- 0.90 for vertebral fracture
- 0.79 for non-vertebral fracture
- 0.71 for palliative radiotherapy
- 0.59 for surgery to the bone
- 0.51 for hypercalcaemia

Direct drug and administration costs are based upon the cost of pamidronate plus an oncology outpatient appointment. The cost per fracture is taken as the average of the relevant inpatient HRGs within NHS reference costs £2,786 [£2,017] with surgery to the bone being costed at £2,813 [£2,036], while radiotherapy is based upon 3 radiotherapy sessions in an outpatient setting to yield a cost of £978 [£708]. Ross and colleagues[55] undertook their own bottom up costing for hypercalcaemia to estimate an average cost of £4,840 [£3,503]. Note that this study was undertaken when discount rates were differentiated between costs at 6% and benefits at 1%.

The model estimates a 4 year survival of 16%, with patients being treated monthly with pamidronate until death or to the end of the fourth year. This results in an average 1.45 SREs being averted compared to BSC: 0.54 non-vertebral fractures, 0.16 vertebral fractures, 0.64 courses of palliative radiotherapy and 0.12 episodes of surgery to the bone. An additional 0.34 episodes of hypercalcaemia are modelled as being prevented together with an average 3.2 months bone pain reduction. The total cost of therapy is estimated to be £7,235 [£5,237] but cost offsets reduce this to £613 [£444]. Excluding hypercalcaemia, this results in a cost per SRE avoided of £423[£306]. With the application of a 0.33 QALY loss per SRE drawn from Dranitsaris and colleagues[169] as reviewed above but adjusted for an increased SRE duration of 22 months, this translates into a cost effectiveness estimate of £1,851 [£1,340] per QALY gained.

Reed and colleagues[A] compare the cost effectiveness of zoledronic acid with BSC for prostate cancer patients with bone metastases, mainly within the context of the USA and Medicare.[171] This analyses within trial SRE rates and resource utilisation data over 15 months to estimate the cost per SRE avoided. An additional cost utility analysis is conducted based upon the EQ-5D VAS scores. The average number of SREs within the zoledronic acid group is 0.78 compared to 1.24 in the BSC group, resulting in ICERs of £11,137 [$12,300] per SRE avoided and £105,976 [US$159,200] per QALY.

De Cock and colleagues[172] model the cost effectiveness of oral ibandronate compared to zoledronic acid and pamidronate among UK breast cancer patients receiving hormonal therapy. Treatment with oral ibandronate is estimated to result in a direct utility gain of 0.02 compared to intravenous administration. Discontinuation rates are also assumed to be lower with 96.9% of ibandronate patients being estimated to be treated for an average of 7.2 months out of a total survival of 14.3 months. This is compared to 71% for zoledronic acid and 73% for pamidronate, though 12% of these patients switch to oral ibandronate. Oral ibandronate is estimated to be as effective as zoledronic acid for those on therapy in preventing SREs, which both are slightly superior to pamidronate. Given this, ibandronate is estimated to yield an additional 0.02 QALYs over both zoledronic acid and pamidronate, while saving £390 [£307] and £201 [£158] respectively.

[A] Supported by Novartis

In a parallel paper, De Cock and colleagues[173] model the cost effectiveness of oral ibandronate compared to zoledronic acid and pamidronate among UK breast cancer patients receiving chemotherapy. This applies the same SRE rates and relative risks for those on therapy as those applied in De Cock and colleagues,[172] with the same discontinuation rates and percentages switching to oral ibandronate. There is also the same anticipated average survival of 14.3 months and the same quality of life values. There is the same average gain from ibandronate of 0.02 QALYs compared to zoledronic acid and pamidronate, but the costs savings differ marginally: £490 [£386] compared to zoledronic acid and £285 [£224] compared to pamidronate.

Guest and colleagues[B] undertake a cost minimisation analysis of pamidronate compared to zoledronic acid for breast cancer patients in the UK, with a one year time horizon.[174] This draws clinical effectiveness estimates from the literature, distinguishing between those on chemo therapy and those on hormonal therapy. Pamidronate is estimated to be marginally superior in preventing any SRE among the chemotherapy group, and slightly inferior to zoledronic acid in preventing any SRE among the hormonal therapy group. These rates are then qualified by rates of individual SREs, with pamidronate typically resulting in slightly more of all SREs among those experiencing an SRE, with the exception of fractures among those receiving hormonal therapy. Pamidronate has a higher discontinuation rate, particularly among those being treated with hormonal therapy. For chemotherapy treated patients, this results in an average 3.77 SREs for pamidronate compared to 2.79 for zoledronic acid. For hormone treated patients, this resulted in an average 3.44 SREs for pamidronate compared to 2.93 for zoledronic acid. The authors conclude that there is little clinical difference, and that as a consequence cost minimisation is appropriate.

Drug administration times for the base case are estimated as 184 to 214 minutes for pamidronate compared to 204 to 232 for zoledronic acid, though this latter includes patients waiting 90 minutes for test results. It is unclear quite how this has been costed. Expert opinion supplies much of the resource use estimates as below.

[B] Supported by Mayne Pharma

**Table 59 UK SRE resource use: Guest and colleagues[174]**

| | Hypercalcaemia | Vert Fracture | Non Vert Fracture | SCC |
|---|---|---|---|---|
| **Inpatient** | 31% for 3 days<br>- 33% oncology<br>- 67% general ward | 45% for 10 days<br>- 17% oncology<br>- 17% orthopaedic<br>- 66% general ward | 20% for 7 days<br>- 70% oncology<br>- 15% orthopaedic<br>- 15% general ward | 31% for 20 days<br>- 83% oncology<br>- 17% general ward |
| **Outpatient** | 2 oncology OP appt | 2 oncology OP appt | 2 oncology OP appt | 2 oncology OP appt |
| **Radiotherapy** | 12% of patients | 79% of patients | 85% of patients | 75% of patients |
| **Surgery** | 1% of patients | 42% of patients | 7% of patients | 19% of patients |

In the light of the above, pamidronate is estimated to be cost saving compared to zoledronic acid: £1,130 [£936] for chemotherapy patients and £776 [£643] for hormonal treated patients.

Reed and colleagues[C] compare the costs and consequences of zoledronic acid with pamidronate among breast cancer patients with bone metastases, again mainly within the context of the USA and Medicare.[171] This analyses within trial SRE rates and resource utilisation data, with a mean patient follow up of 10 months. Zoledronic acid is estimated to have a relative risk of an SRE of 0.80 compared to pamidronate. Costs in the zoledronic acid are estimated to be marginally higher: £14,218 [US$15,703] compared to £14,198 [US$15,680] for pamidronate. This was not taken through to a cost effectiveness estimate specific to breast cancer patients.

Botteman and colleagues[D] compare the cost effectiveness of zoledronic acid, oral ibandronate, intravenous ibandronate, pamidronate, oral clodronate and BSC for breast cancer patients with bone metastases.[175] This uses a cost utility model from a UK NHS perspective, with a monthly cycle over a ten year time horizon. Patients can discontinue active therapy due to non-compliance, which might be due to an adverse event. 50% of those discontinuing move onto another active therapy: oral if previously on intravenous and intravenous if previously on oral. Disease progression is also assumed to lead to therapy being stopped.

A baseline annual rate of 3.05 SREs is assumed for BSC, with this being multiplied by the relevant hazard ratio to arrive at the treatment specific SREs rates: 0.56 for zoledronic acid, 0.62 for oral ibandronate, 0.71 for intravenous ibandronate and 0.70 for pamidronate.

[C] Supported by Novartis
[D] Authorship includes an employee of Novartis

Quality of life values for without an SRE and with an SRE are drawn from the Dranitsaris and colleagues paper[169] on the grounds that is was the only published source available. There is some arbitrariness in the estimation of benefits, with the oral ibandronate being assumed to be postponed to the twelfth week, while oral clodronate was assumed to have half the benefits of the other therapies. Survival was unaffected by treatment, with a mean survival of 20 months.

Zoledronic acid is estimated to require 11 minutes of physician time, 11 minutes of pharmacy technician time and 44 minutes of nurse time, in contrast to 8, 12 and 152 minutes for pamidronate and 10, 11 and 98 minutes for intravenous ibandronic acid. This results in staff administration costs of £42.17 [£37.42] for zoledronic acid, £88.23 [£78.29] for pamidronate and £65.20 [£57.85] for intravenous ibandronic acid.

SRE costs are averaged across the SREs, with an average inpatient cost of £2,272 [£2,016] plus an additional average of £1,826 [£1,620] outpatient and care in the community costs. These are stated as being based upon the Ross and colleagues 2004 bisphosphonates review HTA monograph.[55]

The base case results are an average 6.11 SREs for BSC, with this being reduced to: 3.71 SREs for zoledronic acid; 4.41 SREs for pamidronate; 4.46 for intravenous ibandronate; and, 4.06 for oral ibandronate with this latter possibly being due to the high discontinuation rate and second line intravenous therapy. Given the figure for BSC and the average survival of 2 years, it is not obvious how progression was included in the modelling.

Average QALYs estimates are surprisingly similar between the bisphosphonates: 1.18 QALYs to 1.20 QALYs compared to 0.99 QALYs for BSC. Total costs are £21,032 [£18,662] for BSC, with pamidronate and intravenous ibandronate exceeding this by £127 [£113] and £516 [£458] respectively to yield cost effectiveness estimate relative to BSC of £658 [£584] per QALY and £2,671 [£2,370] per QALY. Zoledronic acid and oral ibandronate are estimated to save £2,554 [£2,267] and £2,382 [£2,114] compared to BSC, and so dominate it, with zoledronic acid further dominating oral ibandronate. Across the therapies, zoledronic acid is estimated to be the preferred treatment at all values of willingness to pay.

Joshi and colleagues[E] estimate the cost effectiveness of zoledronic acid compared to BSC for NSCLC patients across five European countries in what appears to be an update of the Botteman 2009 abstracts, as summarised below.[176-182] This is based upon the NSCLC subset of the phase III trial populations, within which the median survivals were not statistically difference between zoledronic acid, 201 days, and BSC, 157 days. As a consequence, a weibull is fitted to the zoledronic acid arm to yield an estimated average survival of 272 days. This is then multiplied by each arm's SRE specific SMR to derive the number of SREs: 1.38 for zoledronic acid and 2.17 for BSC, though this latter includes some episodes of hypercalcaemia.

SREs are assumed to be associated with only one month loss of quality of life, the baseline NSCLC HRQoL of 0.63 being reduced by 6.8% by vertebral fracture, 20% by non-vertebral fracture, 40% by radiation therapy, 60% by surgery to the bone and 80% by both spinal cord compression and hypercalcaemia as drawn from Hillner and colleagues.[170] This results in zoledronic acid being estimated to yield 0.44 QALYs compared to 0.42 QALYs for BSC.

For the UK, in common with the approach of the 2004 Ross HTA monograph,[55] the costs per SRE were derived mainly from averaging a range of HRG costs. This yields costs of; £138 [€187] for vertebral fracture; £4,520 [€6,105] for non-vertebral fracture; £745 [€1007] for radiation to the bone; £2,456 [€3,318] for surgery to the bone; £3,714 [€5,017] for spinal cord compression; and, £3,822 [€5,163] for hypercalcaemia. Administration costs and supplies for zoledronic acid are based upon the micro costing of DesHarnais and colleagues[183] with 11 minutes physician time, 11 minutes pharmacist time and 44 minutes nurse time to yield a total administration cost of £38.82 [€52.43]. Total UK costs are reported as £3,062 [€4,136] for zoledronic acid compared to £3,086 [€4,168] which suggests a small net saving from zoledronic acid of £22 [€32], though the paper reports this as a saving of £155 [€209]. The 0.79 fewer SREs are estimated to provide cost offsets of £1,217 [€1,787], and zoledronic acid is estimated to dominate BSC for NSCLC patients with bone metastases.

Carter and colleagues[F] model the cost effectiveness of zoledronic acid versus BSC for prostate cancer patients in the France, Germany, Portugal and the Netherlands.[184] Quality of life data is drawn from the Reed and colleagues [185] paper through a back calculation using the ICER and the estimated additional costs. This suggests an average gain from zoledronic acid over placebo of 0.034 QALYs. Rates of individual SREs are estimated solely to inform the drug and SRE costing exercise attached to this estimate of QALY gains. The base case results are that 0.759 SREs are avoided on average, generating savings of between £2,094 [€2,396] and £3,162 [€3,617] per patient. The direct drug and administration costs of zoledronic acid are less geographically variable at between £3,012 [€3,446]

[E] These including Botteman and a Novartis employee
[F] A similar authorship list to Joshi and colleagues 2011 NSCLC paper, and with the support of Novartis

and £3,269 [€3,704], with the resulting increase in costs leading to cost effectiveness estimates ranging from a low of £2,124 [€2,430] in the Netherlands, to a high of £31,476 [€36,007] in France.

Xie and colleagues[G] estimate the cost effectiveness of denosumab compared to zoledronic acid for patients with hormone refractory prostate cancer patients with bone metastases.[186] This uses a one year markov model with a 13 week cycle. The justification for using a one year time horizon rather than a three year time horizon is the anticipation of zoledronic acid being available in generic form from March 2013. But the analysis is from a USA perspective, and the costs are not particularly relevant. The paper is of interest in part because in addition to modelling rates of SREs, the probability of an SRE is dependent upon whether the patient is progression free or with progression. The likelihood of progression is not differentiated by treatment arm, but progression increases the rate of SREs by 2.14 compared to the without progression SRE rate, as drawn from Tchekmedyian and colleagues.[187] Among those without progression denosumab was estimated to have a relative risk of 1st on study SRE of 0.83 and a hazard ratio of 0.82 for subsequent SREs, with these estimates probably being carried over to the with progression patients.

**Table 60 Cost effectiveness in prostate cancer results Xie and colleagues[186]**

| **1 year time horizon** | **Zoledronic Acid** | **Denosumab** | **Net** |
|---|---|---|---|
| **Drug & administration** | £6,734 [$10,960] | £11,815 [$19,230] | £5,081 [$8,270] |
| **Total cost** | £16,914 [$27,528] | £21,714 [$35,341] | £4,800 [$7,813] |
| **SREs** | 0.60 | 0.49 | -0.11 |
| **ICER** | | | £43,641 [$71,027] |
| **3 year time horizon** | **Zoledronic Acid** | **Denosumab** | **Net** |
| **Drug & administration** | £12,271 [$19,972] | £21,532 [$35,044] | £9,261 [$15,072] |
| **Total cost** | £34,169 [$55,612] | £42,683 [$69,468] | £8,513 [$13,856] |
| **SREs** | 1.46 | 1.18 | -0.28 |
| **ICER** | | | £31,532 [$51,319] |

These cost effectiveness results are summarised below, within which unless otherwise stated the cost effectiveness estimates are the cost per QALY for the more effective treatment over the less effective treatment.

[G] Supported by Novartis

**Table 61 Summary of cost effectiveness studies**

| | | | | | SREs | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Main author** | **Year** | **Cancer** | **Country** | **Horizon** | **Deno** | **Z. Acid** | **Pam** | **Oral Ib.** | **BSC** | **Cost per QALY or other c/e** |
| [C]**Dranitsaris**[169] | 1999 | Breast | Canada | 12 mths | | | n.a. | | n.a. | £11,740 [CND$18,700] public TTO<br><br>£10,359 [CND$16,500] expert TTO |
| [Bb]**Hillner**[170] | 2000 | Breast | USA | 2 year | | | 2.09<br>2.60 | | 3.23<br>3.43 | £97,973 [US$108,200] chemo patients<br>£276,444 [US$305,300] hormone patients |
| [A]**Ross**[55] | 2004 | Breast | UK | 4 yr | | | 5.68 | | 7.47 | £1,851 [£1,340] |
| [C]**Reed**[185] | 2004 | Prostate | USA | 15 mths | | 0.78 | | | 1.24 | £11,137 [US$12,300] per SRE |
| [E]**De Cock**[172] | 2005a | Breast | UK | Lifetime | | 2.00 | 2.49 | 2.00 | | Oral ib. dominant in chemo patients<br>saving £390 [£307] versus ZA<br>saving £201 [£158] versus Pam |
| [E]**De Cock**[173] | 2005b | Breast | UK | Lifetime | | 2.00 | 2.10 | 2.00 | | Oral ib. dominant in hormone patients<br>saving £490 [£386] versus ZA<br>saving £285 [£224] versus Pam |
| [D]**Guest**[174] | 2005 | Breast | UK | 1 year | | <br>2.79<br>2.93 | <br>3.77<br>3.44 | | | Cost minimisation: Pam cost saving<br>saving £1,130 [£936] chemo patients<br>saving £776 [£643] hormone patients |
| [C]**Botteman**[175] | 2006 | Breast | UK | 10 yrs | | 3.71 | | | 6.11 | Dominant £2,554 [£2,267] cost saving |
| [C]**Joshi**[182] | 2011 | Lung | UK + 4 EU | 0.75yr av. OS | | 1.44 | | | 2.01 | Dominant £155 [€209] UK cost saving |

| | | | | | SREs | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Main author** | **Year** | **Cancer** | **Country** | **Horizon** | **Deno** | **Z. Acid** | **Pam** | **Oral Ib.** | **BSC** | **Cost per QALY or other c/e** |
| | | | | | | | | | | |
| [C]**Carter**[184] | 2011 | Prostate | Netherlands<br>Portugal<br>Germany<br>France | | | 0.83 | | | 1.59 | £2,124 [€2,430]<br>£7,565 [€8,655]<br>£20,614 [€23,582]<br>£31,476 [€36,007] |
| [C]**Xie**[186] | 2011 | Prostate | USA | 1 year<br>3 year | 0.49<br>1.18 | 0.60<br>1.46 | | | | £43,641 [US$71,027] per SRE avoided<br>£31,532 [US$51,319] per SRE avoided |

[A] No stated interest

[Bb] No stated interest, supported in part by Faculty Research Award from American Cancer Society

[C] Novartis, manufacturer of zoledronic acid

[D] Mayne Pharma, manufacturer of pamidronate

[E] Roche, manufacturer of ibandronic acid

*Available only as abstracts*

A number of other papers available only as abstracts were identified by the literature review. Few details are provided within the abstracts and the results for zoledronic acid compared to BSC, or for denosumab versus zoledronic acid, are summarised below for completeness. Note that all these studies are supported by Novartis. The assessment group has also been in contact with John Carter of Pharmerit with a view to accessing the full texts of the two cost utility studies of denosumab versus zoledronic acid. Apparently these are ready for full publication and will be made available, but are yet to be received by the AG.

**Table 62 Summary of cost effectiveness abstracts**

| | | | | | SREs | | | |
|---|---|---|---|---|---|---|---|---|
| **Lead author** | **Year** | **Cancer** | **Country** | **Horizon** | **Deno** | **Z Acid** | **BSC** | **Cost per QALY or other c/e** |
| **Botteman**[188] | 2005 | Breast | Germany | Lifetime | | 3.95 | 5.62 | £21,424 [€26,795] |
| **Botteman**[177] | 2009 | Lung | UK + 4 EU | Lifetime | | 1.32 | 2.07 | Dominant £209 [€219] UK saving |
| **Botteman**[189] | 2009 | Lung | UK, Fr, Ger | Lifetime | | 1.32 | 2.07 | Dominant £386 [€417] UK saving |
| **Botteman**[181] | 2009 | Renal | UK, Fr, Ger | Lifetime | | 0.66 | 1.74 | Dominant £711 [£699] UK saving |
| **Botteman**[190] | 2010 | Prostate | | 15 mths | | 0.83 | 1.66 | Dominant |
| | | | Netherlands | | | | | |
| | | | Portugal | 15 mths | | 0.83 | 1.66 | Dominant |
| | | | France | 15 mths | | 0.83 | 1.66 | £25,281 [€28,648] |
| | | | Germany | 15 mths | | 0.83 | 1.66 | £13,916 [€15,770] |
| [A]**El Ouagari**[191] | 2005 | Breast | Canada | Lifetime | | 3.44[B] | | Dominant over other bisph. |
| [A]**Meijboom**[192] | 2009 | Prostate | France | 15 mths | | 0.83 | 1.66 | £26,541 [€28,648] |
| | | | Germany | 15 mths | | 0.83 | 1.66 | £8,572 [€9,252] |
| [A]**Carter**[184] | 2011 | Breast | USA | 28 mths | 0.69 | 1.01 | | £395,459 [US$643,626] |
| [A]**Snedecor**[193] | 2011 | Prostate | USA | 27 mths | 1.04 | 1.29 | | £766,831 [US$1,248,051] |
| **Yu**[194] | 2011 | Prostate | USA | 1 year | 0.56 | 0.67 | | £43,756 [US$66,864] per SRE |

[A] co-authored with Botteman

[B] discounted

Note that some abstract that were identified; e.g. Stephens for lung,[195] simply report the results available in other abstracts, in this case Botteman[189] for lung, and are not repeated in the above.

### *11.1.3 Results - quality of life studies*

Clohisy and colleagues[196] use the SF-36 to estimate the quality of life impacts of surgery for skeletal metastases among 52 US patients, of whom 39 completed the preoperative questionnaire and 23 completed the questionnaire 6 weeks subsequent to surgery, this rate falling to 10 questionnaire completions at the 1 year point. The SF-36 scores over time across a range of dimensions as below.

**Table 63 Clohisy[196] SF-36 values for surgery to the bone**

| | Pre-operative | 6 weeks post | 3 months post | 6 months post | 1 year post |
|---|---|---|---|---|---|
| **Physical functioning** | 21.7 | 22.8 | 25.1 | 36.9 | 38.5 |
| **Role-physical** | 2.9 | 4.7 | 4.5 | 9.4 | 16.3 |
| **Bodily pain** | 20.4 | 36.4 | 45.2 | 47.8 | 50.6 |
| **General health** | 45.0 | 44.3 | 39.7 | 42.3 | 50.3 |
| **Vitality** | 27.1 | 33.0 | 37.0 | 42.3 | 50.0 |
| **Social functioning** | 39.1 | 48.4 | 47.7 | 62.5 | 68.8 |
| **Role-emotional** | 24.8 | 29.0 | 17.4 | 33.3 | 16.7 |
| **Mental health** | 54.3 | 55.7 | 61.7 | 62.0 | 50.4 |

These values are not readily translatable into quality of life values. The high rate of attrition in the rate questionnaire completion rate may also call into question the reliability of extrapolation from the pre-operative through to the post-operative.

Falicov and colleagues[35] also investigate the quality of life impacts of surgery for skeletal metastases at the same time points as Clohisy and colleagues[196] but using the EORTC QLQ-C30, the HUI and the EQ-5D among 85 Canadian patients with an average age of 58.6 years. Median survival was a little less than one year. EQ-5D data is available from 77 of these patients and is valued using the UK social tariff to provide a histogram of the number of patients in the first post-operative year in 0.1 QALY ranges, from -0.2 to -0.1 QALYs (1 patient) through to near full health 0.9 to 1.0 QALY (2 patients).

The resulting distribution is strongly bimodal with peaks at 0.0 to 0.2 QALYs and 0.6 to 0.7 QALYs, with an implied global average of 0.26 QALYs. It appears that the lower peak and the implied average

first year QALY may be in large part determined by survival. The results are not easily amended for this, though the second peak at 0.6 to 0.7 QALYs cannot be entirely discounted. Possibly due to patient numbers these results are not further analysed by cancer type.

As summarised in the Matza and colleagues ASCO abstract,[197] judging from the authorship list it appears that Amgen has commissioned a time trade off study among 126 members of the UK general public to estimate the disutilities arising from a number of SREs: spinal cord compression without paralysis, spinal cord compression with paralysis, pathological fracture of the rib, pathological fracture of the arm and pathological fracture of the leg, radiation to the bone over two weeks with 10 administrations, radiation to the bone with only two administrations, and surgery to the bone. This involves assessing a two year lifespan with cancer and bone metastases, with subsequent assessment of this health state with the various SREs added to it. The base health state utility has a mean estimate of 0.47. The abstract reports the SRE disutilities as QALYs, while the electronic copy of the model submitted by the manufacturer reported these as utility decrements and reconstructs the QALY decrement on the assumption that they apply for 11 months. Note that the Amgen model when applying the TTO values also assumes that vertebral fracture has the same disutility as the average across pathological fractures to the rib, arm and leg.

**Table 64 Matza[197] and Amgen model TTO QALY losses for SREs**

| | **Abstract** | **Model[H]** |
|---|---|---|
| **SCC no paralysis** | 0.68 | 0.269 |
| **SCC with paralysis** | 0.44 | |
| **Vertebral fracture** | n.a. | 0.036 |
| **Non-vertebral fracture** | 0.07 | 0.036 |
| **2 weeks radiation** | 0.10 | 0.038 |
| **2 radiation administration** | 0.05 | |
| **Surgery to the bone** | 0.14 | 0.071 |

Prof. John Brazier was involved in the study and has been approached by the AG with a view to accessing the full paper. Prof. Brazier passed this request to Amgen in mid-September 2011. There is little detail on the TTO exercise within the published abstract. It appears that the Amgen modelling may have taken the two year QALY loss and broadly have converted it pro rata to an 11 month QALY loss. Whether this is correct within the context of the TTO exercise is impossible to tell from the published abstract.

[H] Assumes SRE experienced for 11 months

Miksad and colleagues,[I] estimate the quality of life impact from the various stages of ONJ:[198] stage 0 with no evidence of necrotic bone, stage 1 with exposed or necrotic bone but no infection, stage 2 with infection, pain and erythema and stage 3 with pathological fracture, extra oral fistula or osteolysis. Of the 54 cancer patients with ONJ contacted by phone, 34 agreed to undertake questionnaires to assess quality of life by the VAS, TTO with a horizon of 48 weeks and EQ-5D over the phone.

**Table 65 Miksad[198] utility decrements from ONJ**

| | | ONJ decrements | | |
|---|---|---|---|---|
| | **Stage 0** | **Stage 1** | **Stage 2** | **Stage 3** |
| **VAS** | 0.76 | -0.10 | -0.33 | -0.51 |
| **TTO** | 0.86 | -0.05 | -0.22 | -0.29 |
| **EQ-5D** | 0.82 | -0.05 | -0.33 | -0.61 |

Within a cost utility analysis of palliative radiotherapy, van den Hout and colleagues[199] estimate the quality of life among 1,157 patients with bone metastases from the primary cancers: 39% breast cancer patients, 25% lung cancer patients, 23% prostate cancer patients and 13% other cancers. This applies the EQ-5D valued using the UK social tariff. Limited quality of life differences are found between different methods of delivering radiotherapy, which is the focus of the paper. But for current purposes the evolution of the average quality of life may be of more immediate interest. Van den Hout[199] provides a graph of the evolution of quality of life prior to death, with the value being relatively constant at around 0.60 in the penultimate year, but declining in a concave fashion over the year prior to death. This is admittedly average across a range of cancers and van den Hout[199] does not report the number of questionnaires available for each time point, but it may be an important qualifier to any modelling.

[I] with some indeterminate support from Pfizer and Merck, possibly institutional

**Table 66 van den Hout[199] quality of life values in last year of life – from graph**

| Months to death | Utility | Multiplier |
|---|---|---|
| 1 | 0.20 | 34% |
| 2 | 0.25 | 43% |
| 3 | 0.30 | 52% |
| 4 | 0.33 | 57% |
| 5 | 0.37 | 63% |
| 6 | 0.40 | 69% |
| 7 | 0.40 | 69% |
| 8 | 0.43 | 74% |
| 9 | 0.45 | 78% |
| 10 | 0.48 | 83% |
| 11 | 0.53 | 91% |
| 12 | 0.58 | 100% |

Weinfurt and colleagues[J] estimate the quality of life impact of the 1st on study SRE among 248 prostate cancer patients who experienced at least one SRE during a zoledronic acid RCT:[129] radiation to the bone, pathological fracture and other 1st on study SREs. Pooling of the SREs other than radiation and pathological fracture may have been necessary due to the small sample size. For each SRE only patients who experience it as their 1st on study SRE are included. The EQ-5D data is valued using the UK social tariff. The analysis apparently controls for other patient characteristics, with the pre and post SRE levels being characterised by assessments up to 100 days prior to the SRE and 100 days post. Prior to any on study SRE the baseline average quality of life is 0.70. The first on study SREs are associated with the following decrements at the first HRQoL measurement within 100 days of SRE diagnosis:

- Radiation to the bone -0.07
- Pathological fracture -0.13
- Other SREs pooled -0.02

[J] A named author being employed by Novartis with an additional grant for the study being given by Novarti

**Table 67 SRE quality of life values**

| Main Author | Year | Method | Estimate | SRE type | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | V Frac | NVFrac | Rad. | Surgery | SCC | Other[A] | Any |
| **Darnitsaris**[169] | 1999 | TTO general public | HRQoL loss while on pamidronate | | | | | | | -0.19 |
| | | TTO experts | HRQoL loss while on pamidronate | | | | | | | -0.43 |
| | | TTO general public | HRQoL loss while on BSC | | | | | | | -0.26 |
| | | TTO experts | HRQoL loss while on BSC | | | | | | | -0.31 |
| **Hillner**[170] | 2000 | Expert opinion | HRQoL loss (assumed 1 month duration) | -0.20 | -0.20 | -0.40 | -0.60 | -0.80 | | |
| **Reed**[185] | 2004 | Patient EQ-5D VAS | HRQoL loss within ± 30 days of SRE | | | | | | | 0.07 |
| | | | HRQoL loss within ± 60 days of SRE | | | | | | | 0.06 |
| | | | HRQoL loss within ± 90 days of SRE | | | | | | | 0.05 |
| **Falicov**[35] | 2006 | EQ-5D UK tariff | QALY for remaining lifetime | | | | 0.26 | | | |
| **Weinfurt**[129] | 2006 | EQ-5D UK tariff | HRQoL loss: measurement ≤ 100 days of SRE | | -0.13 | -0.07 | | | -0.02 | |
| **Matza**[197] | 2011 | TTO UK public | 2 year QALY loss | | -0.07 | -0.10 to -0.05 | -0.14 | -0.44 to -0.68 | | |

[A]Restricted to Weinfurt; i.e. SREs other than non-vertebral fracture and radiation to the bone

### *11.1.4 Results – resource use studies*

*Full papers*

*Resource use: drug and administration costs*

DesHarnais Castel and colleagues[11] provide a USA based micro-costing study of zoledronic acid and pamidronate among patients with metastatic bone disease.[183] This draws data from three outpatient chemotherapy infusion sites, which were also participating in a concurrent zoledronic acid trial. For zoledronic acid average staff times for pre-infusion, preparation and set up, administration and follow up are estimated as 16 minutes, 6 minutes, 40 minutes and 4 minutes respectively to give a total of 66 minutes. For pamidronate the times are 16 minutes, 5 minutes, 148 minutes and 4 minutes respectively, to give a total time of 173 minutes.

Barrett-Lee and colleagues[12] provide a UK based study of the costs of administering intravenous bisphosphonates among breast cancer patients with bone metastases.[200] This is across three cancer centres, with the first 50 administrations from the start of study being analysed through audit forms. Only 71% of the completed forms relate to breast cancer patients, and results are only reported for these patients. Zoledronic acid provided 67% of administrations, with the vast majority of the remainder being pamidronate. Zoledronic acid is reported as taking an average 4 minutes preparation time coupled with 18 minutes administration time, though it is not clear whether this is patient time or staff time. Pamidronate is reported as requiring 4 minutes and 93 minutes respectively. Perhaps the most relevant statistic is that 77% of the breast cancer patients receiving a bisphosphonate infusion were making a hospital visit solely for this purpose.

Oglesby and colleagues[13] undertake a time and motion study of the time and costs of administering zoledronic acid among 42 breast cancer patients and 26 prostate cancer patients in the USA.[201] This concludes that among patients not receiving chemotherapy the overall mean time per administration was 1 hour 9 minutes, while among patients receiving chemotherapy it was 3 hours 1 minute, though this latter includes 1 hour 15 minutes specific to the chemotherapy infusion. The average across patients was a little under two hours.

Houston and colleagues,[14] within a UK based study of renal function changes and NHS resource use among 189 patients, estimate an average staff time per zoledronic acid administration of 28 minutes, compared to 6 minutes for oral ibandronate.[149]

[11] Supported by Novartis
[12] Supported by Roche
[13] Supported by Amgen
[14] Supported by Roche

*Resource use: SREs and adverse events*

Malmberg and colleagues[202] in a Netherlands based cost effectiveness study of adding strontium 89 to external radiotherapy among prostate cancer patients estimate the average cost per radiotherapy episode as £5,382 [SEK31,011] for those in county, and £8,433 [SEK48,585] for those out of county, this latter figure being higher due to the higher rate of inpatient admissions.

Groot[203] estimate the resource use associated with SREs among 28 prostate cancer patients in the Netherlands over a two year period, during which 61 SREs are experienced. The majority of SREs are radiotherapy to the bone, most of which are treated as outpatient procedures.

**Table 68 Groot[203] SRE resource use in Dutch prostate cancer patients**

| **Outpatient** | **SREs** | | | | **Treatment Cost** | | **Total Cost** | |
|---|---|---|---|---|---|---|---|---|
| External bean RT | 25 | | | | £1,033 | € 1,187 | £1,033 | € 1,187 |
| Strontium 89 | 21 | | | | £1,579 | € 1,815 | £1,579 | € 1,815 |
| **Inpatient** | | **LoS** | **Inpatient Cost** | | **Treatment Cost** | | **Total Cost** | |
| External bean RT | 3 | 12 | £3,091 | € 3,553 | £1,033 | € 1,187 | £4,124 | € 4,740 |
| Pain management and RT | 1 | 22 | £5,667 | € 6,514 | £1,033 | € 1,187 | £6,700 | € 7,701 |
| SCC and RT | 4 | 29 | £7,534 | € 8,660 | £1,033 | € 1,187 | £8,567 | € 9,847 |
| Hip operation | 2 | 14 | £3,477 | € 3,997 | £1,074 | € 1,234 | £4,551 | € 5,231 |
| Hip operation with CC | 1 | 129 | £33,231 | € 38,196 | £2,394 | € 2,752 | £35,625 | € 40,948 |
| Fixation of femour fracture | 1 | 16 | £4,121 | € 4,737 | £965 | € 1,109 | £5,086 | € 5,846 |
| Pain management and RT | 3 | 10 | £2,576 | € 2,961 | | | £2,576 | € 2,961 |

Delea and colleagues[15] estimate the costs associated with SREs among 534 USA lung cancer patients using data from an insurance claims database.[204] The average SRE related costs over a 3 year time horizon is estimated as £7,974 [US$11,979] with 90% of this occurring within 2 months of the first claim.

Delea and colleagues[16] in a similar analysis estimate the costs associated with SREs among 617 USA breast cancer patients with bone metastases through a matched pairs analysis of an insurance claims

[15] Supported by Novartis
[16] Supported by Novartis

database, of whom 52% experienced at least one SRE.[205] The average lifetime treatment cost of SREs is £8,981 [US$13,940]. Other costs are also higher in the SRE patient group, by £22,055 [US$34,233] with the average increase among SRE patients being £31,036 [US$48,173].

Lage and colleagues[17] undertake a retrospective analysis of a USA insurance claims database to estimate the costs of SREs among prostate cancer patients.[206] The average annual costs per individual SRE are: radiotherapy: £3,143 [US$5930]; fracture: £1,685 [US$3179]; surgery to the bone: £1,176 [US$2218]; and, spinal cord compression: £244 [US$12469]. The annual average per patient is calculated as £6,609 [US$12469].

Barlev and colleagues[18] estimate the direct inpatient costs arising from pathological fracture, surgery to the bone and spinal cord compression among multiple myeloma, prostate cancer patients with bone metastases and breast cancer patients with bone metastases through a USA Medicare related database.[207] For prostate cancer patients the average inpatient costs for pathological fracture, surgery to the bone and spinal cord compression are £14,652 [US$22,390], £27,546 [US$42,094] and £39,125 [US$59,788] respectively, while for breast cancer patients they are £17,627 [US$26,936], £22,735 [US$34,742] and £39,194 [US$59,894].

## 11.2 Critique of the manufacturer's submission

### *11.2.1 Patient groups, indications and comparator treatments*

The comparators for each cancer are chosen by the manufacturer partly in the light of NICE clinical guidelines. But current prescribing patterns as identified through a manufacturer commissioned patient chart review coupled with drug use data sourced from the IMS oncology organizer also help determine these[19].

For breast cancer, the NICE guideline[45] recommends consideration of bisphosphonates for patients diagnosed with bone metastases. This is reflected in the manufacturer prescription data, within which zoledronic acid is the most frequently used bisphosphonate. In the light of this zoledronic acid is chosen as the primary comparator for breast cancer.

But note that this does not preclude consideration of patient subgroups: the cost effectiveness of denosumab among patients who are SRE naïve at baseline may differ from that for those who are SRE experienced at baseline. It may also be appropriate to consider best supportive care as a comparator

[17] Supported by Amgen
[18] Supported by Amgen
[19] It appears that the prescribing and treatment data of tables 13 and 14 is specific to UK patients.

for those contraindicated to bisphosphonates. The manufacturer case review concluded that 8% of breast cancer patients with bone metastases will probably never be treated with bisphosphonates.

For prostate cancer, the NICE guideline[46] only recommends consideration of bisphosphonates for pain relief when other conventional analgesics and palliative radiotherapy have failed. The manufacturer case review suggests that 49% of prostate cancer patients have received bisphosphonates. 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. The case review also suggests an additional 19% of patients are likely to receive bisphosphonates in the future. Within this, zoledronic acid is the main drug, with over 90% market share. The manufacturer uses this to split the analysis into SRE naïve patients, for whom the comparator is BSC, and SRE experienced patients which is used as a proxy for uncontrolled pain, for whom the primary comparator is zoledronic acid.

For lung cancer, the NICE guideline[48] does not recommend the use of bisphosphonates. The metastatic spinal cord compression guideline provides similar recommendations for breast cancer and for prostate cancer to the cancer specific guidelines summarised above. But it adds to this that bisphosphonates should not be used in other cancers to treat spinal pain with the intention of preventing metastatic spinal cord compression except as part of an RCT. Despite this, the manufacturer case review suggests that 37% of other solid tumour patients have been treated with bisphosphonates, with another 13% likely to receive them in the future. Again, 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. Zoledronic acid is the main bisphosphonate used, with an 80% market share. The manufacturer uses this to split the analysis for other solid tumour patients into SRE naïve patients, for whom the comparator is BSC, and SRE experienced patients, for whom the primary comparator is zoledronic acid.

Within the manufacturer modelling there appears to be no specific consideration of uncontrolled pain from bone metastases despite use of conventional analgesics and palliative radiation therapy to the bone. This subgroup does not appear to have been defined or analysed within the manufacturer analyses. But the manufacturer notes that among prostate patients who were SRE experienced at baseline, 80% also had painful bone metastases at baseline. The corresponding figure for other solid tumour patients is 86%. In the light of this, the manufacturer has taken the subgroup of the SRE experienced at baseline as a proxy for the likelihood of having uncontrolled pain from bone metastases.

**Table 69 Manufacturer primary comparator treatments**

| **Bisph. tolerant** | **Breast cancer** | **Prostate cancer** | **Other solid tumours** |
|---|---|---|---|
| **All patients** | zoledronic acid | not presented | not presented |
| **SRE naive** | not presented | BSC | BSC |
| **SRE experienced** | not presented | zoledronic acid[20] | zoledronic acid[21] |
| **Bisph. contraindicated** | **Breast cancer** | **Prostate cancer** | **Other solid tumours** |
| **All patients** | not presented | not presented | not presented |
| **SRE naive** | not presented | BSC[22] | BSC |
| **SRE experienced** | not presented | zoledronic acid | zoledronic acid |

Given data availability, the additional comparators of disodium pamidronate and ibandronic acid are also considered for breast cancer. Similarly, for other solid tumours data availability permits the consideration of disodium pamidronate as an additional comparator for SRE experienced patients.

### *11.2.2 Manufacturer model structure summary*

The manufacturer separately models three cancer groups: breast cancer, prostate cancer and all other solid tumours including lung cancer. While the parameter inputs to the modelling of the three cancers differ, the model structure is essentially the same across the three cancers: a cost-utility markov model; a 4 week cycle to reflect dosing frequency; and, a ten year time horizon for the base case. The assessment group judges the manufacturer model to be of good quality and structure, and rebuilds it with some structural additions for its own economic analysis. As a consequence, the manufacturer model is summarised in detail below.

For a given cancer, all patients within the manufacturer model are assumed to have the same survival risk. This is derived from a survival analysis[23] of the denosumab trial data, pooled across the denosumab and zoledronic acid arms. This is augmented by age specific non-cancer deaths drawn from general population data. The reason for augmenting the survival curve estimated from the trial data with age specific non-cancer deaths is not immediately obvious. It may be to help prevent the possible over-extrapolation of survival given the survival curves for breast cancer, prostate cancer and

[20] 80% of these patients are reported as having painful bone metastases at baseline in the denosumab trial
[21] 86% of these patients are reported as having painful bone metastases at baseline in the denosumab trial
[22] As neither the manufacturer or the assessment group have been able to source clinical estimates specific to those contraindicated to bisphosphonates, where comparisons have been presented for denosumab versus BSC this can be taken as the best estimate for the cost effectiveness of denosumab among those contraindicated to bisphosphonates.
[23] Weibull for breast cancer, gamma for prostate cancer and log-logistic for other solid tumours based upon the AIC: Tables 53 and 54 of the manufacturer submission.

other solid tumours in the manufacturer's submission. Or it may be to enable sensitivity analyses around the baseline age to be examined[24].

The key assumption, supported by the clinical trials, is that there is no overall survival difference between denosumab and zoledronic acid, with this assumption of no survival differences also being carried over to the other comparators where applicable. In other words, survival is not affected by rates of SREs.

The manufacturer model divides patients into those who are SRE naïve at start of treatment and those who are SRE experienced at start of treatment. The baseline rates of SREs are drawn from the zoledronic acid arm of the relevant denosumab trial.

- For the SRE naïve, another time to event analysis is undertaken using the time to first on study SRE data from SRE naïve patients in the zoledronic acid arm. The hazard ratios for the other comparators are applied to this to estimate the evolution of first SREs among SRE naïve patients for the comparator arms.
- For the SRE experienced a constant rate of SREs is assumed. This rate is drawn from all on-study SREs among the SRE experienced at baseline. Note that the manufacturer does not include subsequent SREs among those who were initially SRE naïve at baseline. The manufacturer justifies this on the basis that it would break randomisation. It is not clear to the AG why this applies, and including these SREs as a sensitivity analysis may be desirable. Relative risks are applied to this rate to estimate the rates for the comparator arms.

The balance between the different types of SREs is taken from the denosumab trials, pooled across the arms.

Individual SREs are associated with an HRQoL loss estimated using EQ-5D data from the denosumab trials. These estimates are cancer specific, and are summarised in greater detail in section 11.2.3 below. It is assumed that the HRQoL loss associated with an SRE can extend up to 5 months prior to the month of its identification, and up to 5 months subsequent to the month of its identification. This yields an overall absolute QALY decrement for each SRE. A utility level is also estimated for SRE naïve patients, and for SRE experienced patients. SRE naïve patients experiencing an SRE have the SRE experienced utility applied thereafter.

Individual SREs are also associated with a cost. The base case estimates these from a manufacturer commissioned observational study as summarised in greater detail in section 11.2.4 below.

[24] The probabilistic modelling treats the baseline age as being deterministic

Manufacturer expert opinion suggested that vertebral fracture would be asymptomatic to the degree that treatment would be unlikely, and the base case applies no cost to vertebral fractures[25].

Rates of the serious adverse events of ONJ, renal toxicity, hypercalcaemia, hypocalcaemia and skin infections are estimated from the clinical trials separately for denosumab and for zoledronic acid. These are also associated with discontinuation rates as drawn from the clinical trials. Additional non-SAE specific discontinuations are included in the model, with these being the main source of patients discontinuing active treatment for both denosumab and zoledronic acid. The risk of an SRE among those discontinuing is assumed to be equal to that for BSC.

The HRQoL impact of an adverse event draws on the same EQ-5D data as that used for estimating the HRQoL impact of SREs. Note that a unified overall model is not presented, and the data is analysed separately for SREs and for AEs. The assumed duration of HRQoL impacts is lifetime for ONJ and renal toxicity, while the duration of HRQoL impacts from hypercalcaemia, hypocalcaemia and skin infections is as apparently recorded within the individual patient level data.

### *11.2.3 Clinical data and effectiveness*

*Patient characteristics*

Baseline patient characteristics are drawn from the relevant denosumab trials.

**Table 70 Baseline patient characteristics**

| | **Breast cancer** | **Prostate cancer** | **Other solid tumours** |
|---|---|---|---|
| Age | 57 | 71 | 60 |
| Female | 99% | 0% | 36% |
| SRE naive | 59% | 74% | 52% |

*Survival data*

On the basis of the AIC, the survival analysis of the data pooled across the arms of the denosumab trials suggests modelling breast cancer survival using a weibull, prostate cancer using a gamma and other solid tumours using a log-logistic functional form.

[25] 40% to 45% of fractures in breast cancer, 50% to 70% of fractures in prostate cancer and 40% to 50% of fractures in other solid tumours including lung were vertebral fractures.

**Table 71 Overall survival fitted curves**

| | Breast cancer | Prostate cancer | Other solid tumours |
|---|---|---|---|
| **Distribution** | Weibull | Gamma | Log-logistic |
| **Intercept** | 7.2206 | 6.5823 | 5.7772 |
| **Scale** | 0.7775 | 0.9240 | 0.7154 |
| **Shape** | | 0.6243 | |

These survival curves are, for reasons that are not entirely clear, augmented with the age specific non-solid tumour mortality rates as drawn from UK life tables. This results in the following survival percentages within the modelling.

**Table 72 Modelled survival percentages**

| | Breast cancer | | Prostate cancer | | Other solid tumours | |
|---|---|---|---|---|---|---|
| **Year** | **fitted curve** | **+general mort.** | **fitted curve** | **+general mort.** | **fitted curve** | **+general mort.** |
| 1 | 83% | 83% | 68% | 66% | 46% | 46% |
| 2 | 64% | 64% | 41% | 39% | 24% | 24% |
| 3 | 47% | 47% | 25% | 23% | 15% | 15% |
| 4 | 34% | 33% | 15% | 14% | 11% | 11% |
| 5 | 24% | 23% | 9% | 8% | 8% | 8% |
| 6 | 16% | 16% | 6% | 5% | 6% | 6% |
| 6 | 16% | 10% | 6% | 3% | 6% | 5% |
| 7 | 11% | 7% | 4% | 2% | 5% | 4% |
| 8 | 7% | 4% | 2% | 1% | 4% | 3% |
| 9 | 5% | 3% | 2% | 1% | 4% | 3% |
| 10 | 3% | 3% | 1% | 1% | 3% | 3% |

*Balance between types of SREs*

The balance between the different SREs is taken from the denosumab trials, with the data being pooled between the arms. The balance between the SRE types is time invariant, with the exception that once an SRE naïve patient has experienced a first SRE the balance between SREs is that for subsequent SREs as applied to SRE experienced patients.

**Table 73 Balance between SRE types with 21 day window data pooled across the arms**

| | Breast cancer | | Prostate cancer | | Other solid tumours | |
|---|---|---|---|---|---|---|
| | SRE Naive | SRE Exp. | SRE Naive | SRE Exp. | SRE Naive | SRE Exp. |
| Vertebral fracture | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Non-vertebral fracture | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Radiation to the bone | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Surgery to the bone | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Spinal cord compression | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

*Rates of SREs for zoledronic acid*

Zoledronic acid is taken as the numeraire against which the other treatments' hazard ratios and relative risks are measured. The rates of first SREs and subsequent SREs for the comparator treatments are derived through the application of the relevant hazard ratios and relative risks. The rates of SREs for zoledronic acid are split into:

- the time to first on-study SRE for SRE naïve patients, and
- the SRE rate per cycle for patients who are SRE experienced at baseline.

*Times to first SRE among SRE naïve patients*

A reasonably standard set of time to event functional forms are fitted to the time to first on-study SRE among SRE naïve patients for the zoledronic acid arm of the denosumab trials. This results in the log-normal form being assessed as best by the AIC for prostate cancer and other solid tumours.

But the gamma function is estimated as being superior for breast cancer patients with an AIC of 3327 compared to 3330 for the log-normal, which is the next best fit. The manufacturer justifies the adoption of a common log-normal form on the basis of the probabilistic model often simulating a shape parameter for the gamma distribution of less than 0.08 which is apparently problematic. But even if this is the case, it would seem desirable to have applied the fitted gamma function within the deterministic modelling to test any sensitivity to this assumption. Unfortunately, the submission does not outline the parameterised form of the gamma distribution for breast cancer. If the central estimate for this postpones the first SRE beyond that suggested by the fitted log-normal distribution this may have tended to bias the analysis in favour of denosumab. The parameter estimates are as below.

**Table 74 Log-normal parameters for time to first on-study SRE for SRE naive**

| | Breast Cancer | Prostate cancer | Other solid tumours |
|---|---|---|---|
| **Intercept** | 6.8849 | 6.3098 | 6.1074 |
| **Scale** | 1.6315 | 1.4547 | 1.5229 |

*Rates of subsequent SREs among SRE experienced patients*

The SRE cycle rate is calculated as the total number of SREs divided by the patient years of exposure, and adjusted to the 28 day cycle length. The base case applies the 21 day window definition of an SRE which results in the following cycle rates. The manufacturer assumes a cycle lasts 4/52$^{nds}$ of one year within this calculation. This is marginally longer than the true 28/365$^{ths}$ and serves to slightly increase the rate of SREs within the zoledronic arm, but this is unlikely to have much if any material effect upon results.

**Table 75 On-study SRE rates among SRE experienced in zoledronic acid arm with 21 day window**

| | Breast Cancer | Prostate cancer | Other solid tumours |
|---|---|---|---|
| **Patient years exposure** | [redacted] | [redacted] | [redacted] |
| **SREs** | [redacted] | [redacted] | [redacted] |
| **Cycle rate based upon 4/52** | [redacted] | [redacted] | [redacted] |
| **Cycle rate based upon 28/365** | [redacted] | [redacted] | [redacted] |

Note that the SRE rate per cycle for SRE experienced patients excludes the data on SREs subsequent to the first on study SRE among the SRE naïve at baseline patients. The manufacturer justifies this on the grounds that it would break randomisation. This justification is not understood by the assessment group. It could be argued that applying the SRE rate estimated from patients who were SRE experienced at baseline to the patients who were SRE naïve at baseline but have experienced an on-study SRE is a more serious violation of randomisation or stratification within the trials. Note also that the proportions of patients who were SRE naïve at baseline were 59% for breast cancer, 74% for prostate cancer and 52% for other solid tumours.

*Hazard ratios and relative risks for SREs for comparator treatments*

The manufacturer submission applies the hazard rates for time to first on study SRE and relative risks for time to first and subsequent SRE as estimated from the denosumab trial data for denosumab versus zoledronic acid [table 29], and from the network meta-analysis for the other comparators [tables 50, 51 and 52] with zoledronic acid being the numeraire as outlined above. These are summarised below.

**Table 76 Manufacturer hazard ratios and relative risks**

| Submission tables 29, 50, 51 and 52 | Breast cancer | Prostate cancer | Other solid tumours |
|---|---|---|---|
| **TTF HR vs zoledronic acid** | | | |
| Pooled across all patients | | | |
| BSC/Placebo | [redacted] | 1.493 | 1.370 |
| Ibandronic acid | [redacted] | | |
| Disodium pamidronate | [redacted] | | [redacted] |
| Denosumab | 0.820 | 0.820 | [redacted] |
| Denosumab SRE naive | [redacted] | 0.800 | [redacted] |
| Denosumab SRE experienced | [redacted] | [redacted] | [redacted] |
| **RR TTF&Subs vs zoledronic acid** | | | |
| Pooled across all patients | | | |
| BSC/Placebo | [redacted] | 1.563 | 1.366 |
| Ibandronic acid | [redacted] | | |
| Disodium pamidronate | [redacted] | | [redacted] |
| Denosumab | [redacted] | [redacted] | [redacted] |
| Denosumab SRE naive | [redacted] | [redacted] | [redacted] |
| Denosumab SRE experienced | [redacted] | [redacted] | [redacted] |

Note that while the submission suggests that the subgroups of SRE naïve and SRE experienced are analysed separately, the subgroup specific hazard ratios and relative risks for denosumab versus zoledronic acid are not applied. The modelling submitted by the manufacturer applies the hazard ratios and relative risks pooled across all patients, whether modelling SRE naïve patients or SRE experienced patients. This is likely to have mainly affected the cost effectiveness results presented for prostate cancer and for the other solid tumours group.

It would seem sensible to apply the SRE naïve and SRE experienced specific hazard ratios and relative risks for denosumab versus zoledronic acid when analysing these subgroups. The SRE experienced subgroup specific central estimates suggest a smaller effect from denosumab compared to the pooled estimates for these patients.

*Adverse events and discontinuations*

The model includes the following serious adverse events:

- osteonecrosis of the jaw,
- renal toxicity,

- hypercalcaemia,
- hypocalcaemia; and,
- skin infections.

For the main comparators of denosumab and zoledronic acid the rates of these are drawn from the denosumab trials. Each of these serious adverse events is also associated with a treatment specific discontinuation rate, again drawn from the denosumab trials. A further treatment specific general discontinuation rate is drawn from the denosumab trials, though it is not clear whether the definition of this excluded the discontinuations due to serious adverse events. The key assumption within the handling of adverse events and discontinuations is that their rates are constant over the period of the modelling.

**Table 77 Serious adverse events and discontinuations per 28 day cycle**

| | **Breast cancer** | | **Prostate cancer** | | **Other solid tumours** | |
|---|---|---|---|---|---|---|
| | **Per cycle** | **Discs.** | **Per cycle** | **Discs.** | **Per cycle** | **Discs.** |
| **Zoledronic acid** | | | | | | |
| **ONJ** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Renal toxicity** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Hypercalcaemia** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Hypocalcaemia** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Skin infection** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Other discontinuation** | | [redacted] | | [redacted] | | [redacted] |
| **Total per cycle** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Denosumab** | | | | | | |
| **ONJ** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Renal toxicity** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Hypercalcaemia** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Hypocalcaemia** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Skin infection** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Other discontinuation** | | [redacted] | | [redacted] | | [redacted] |
| **Total per cycle** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

The rates of adverse events for the other bisphosphonates are drawn from the literature, and are assumed to apply equally across the three cancers groups being modelled. Discontinuation rates due to

serious adverse events for the other bisphosphonates are assumed to be the average across the rates observed for denosumab and zoledronic acid. Discontinuation rates for the other bisphosphonates not due to serious adverse events are drawn from another three papers within the literature.

Rates of adverse events for BSC are assumed to be zero. This may be unrealistic and may tend to worsen the cost effectiveness estimates for the active treatments relative to BSC. But adverse event rates do not appear to be key model drivers.

Note that those discontinuing denosumab or bisphosphonate therapy are assumed to immediately assume the BSC relative risk for SREs. There is no waning protective effect from having received denosumab or bisphosphonate therapy.

Discontinuations also introduce what may appear to be a perversity within the model structure. The model estimates both denosumab and zoledronic acid to have a very poor cost effectiveness when compared with BSC. Because of this, a treatment which has a high discontinuation rate sees patients rapidly move off active treatment and onto the more cost effective BSC. As a consequence, a high discontinuation rate for an active treatment improves the cost effectiveness estimate for that treatment. This requires some qualification, in that the situation is more complicated if the main sources of discontinuations are SAEs, with their associated HRQoL and cost impacts. But as can be seen from the above, for both denosumab and zoledronic acid the vast majority of discontinuations are not related to SAEs.

#### *11.2.4 Resource use*

The manufacturer undertook a systematic literature review to try to identify the costs associated with SREs and AEs as outlined in the manufacturer submission. Out of the 150 papers identified by the search, 6 were found to have data relevant to the modelling. From these 6 papers, only the cost of treating hypercalcaemia £4,579 [£3,791 in 2004] as drawn from the Ross HTA Monograph[55] is used.

*Drug and administration costs*

The list price of denosumab is £309.86 per vial. 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 which differs slightly from table 72 of the submission, giving the list prices as:

- £174.17 for a 4mg vial of Zometa® zoledronic acid, and
- £165.00 for a 90mg vial of generic pamidronate.

This compares to the respective costs applied by the manufacturer of £183.30 and £167.73. This mainly affects the comparison with zoledronic acid, the manufacturer cost for it being 5% higher than BNF62.

To estimate the administration costs associated with the different administration routes the manufacturer commissioned a micro-costing study, as summarised in the manufacturer's submission. This study was undertaken in the UK among 80 oncology nurses and 20 oncology pharmacists. 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 injections.

Note that the micro-costing study did not estimate the additional nursing time associated with different infusion durations. Infusion nursing time was apparently estimated from the products' SPCs and subsequently confirmed by respondents: 15 minutes for zoledronic acid, 15 minutes of IV ibandronic acid and 90 minutes for disodium pamidronate. These timings were included in the costing.

For the comparison between denosumab and zoledronic acid the main differences in terms of minutes of staff time reported by the oncology nurses and as outlined in the manufacturer's submission were, to the nearest minute:

**Table 78 Drug administration timings and staff costs**

| | Deno. | | Zol. Acid | | Pamid. | | Iban IV | |
|---|---|---|---|---|---|---|---|---|
| | **Mean** | **Median** | **Mean** | **Median** | **Mean** | **Median** | **Mean** | **Median** |
| **Pre-administration** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Drug preparation** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Drug administration** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **of which drug infusion** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Post administration** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Total (minutes)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Total (hours)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Staff cost** | [redacted] | **£33.24** | [redacted] | **£66.28** | [redacted] | **£138.49** | [redacted] | [redacted] |

Due to the apparently highly skewed nature of replies, the manufacturer has chosen to use the medians rather than the means for costing purposes. The requirement to make this adjustment may suggest that the micro-costing study is not entirely reliable. [redacted]

The manufacturer estimates that denosumab will result in staff time savings compared to zoledronic acid of around [redacted] per administration. These arise in part from the pre-administration savings

of about [redacted], but more from drug administration savings of [redacted] within which avoiding the need for infusion saves [redacted] of staff time.

Taking these elements together with the consumables and fixed costs estimated within the micro-costing study yields the total annual direct drug and administration costs as below.

**Table 79 Direct drug and administration costs: 4 weekly dosing**

| | **Denos.** | **Zol. Acid** | **Pamid.** | **Iban IV** | **Iban Oral** |
|---|---|---|---|---|---|
| **Direct Drug Costs per administration** | | | | | |
| Manufacturer BNF | | £183.30 | £167.73 | £183.69 | £183.69 |
| BNF62 | | £174.17 | £165.00 | | |
| Without PAS | £309.86 | | | | |
| With PAS | [redacted] | | | | |
| **Administration** | | | | | |
| Staff time | £33.24 | £66.28 | £138.49 | £66.28 | £4.50 |
| Monitoring cost | £0.00 | £1.41 | £1.41 | £1.41 | £1.41 |
| Consumables | £0.44 | £7.31 | £7.24 | £7.31 | £0.00 |
| Capital costs | £0.06 | £0.52 | £1.84 | £0.52 | £0.00 |
| **Annual totals as per manufacturer** | | | | | |
| Without PAS | £4,466.80 | £3,364.66 | £4,117.23 | £3,369.73 | £2,464.80 |
| With PAS | [redacted] | | | | |
| **Annual totals BNF62** | | | | | |
| Without PAS | £4,466.80 | £3,245.97 | £4,081.74 | £3,369.73 | £2,464.80 |
| With PAS | [redacted] | | | | |

Without the PAS the annual denosumab cost of £4,467 is around £1,102 more expensive than zoledronic acid.

The PAS proposed by the manufacturer has recently been approved. [redacted]

[redacted]

The base case assumes four weekly dosing for both denosumab and the bisphosphonates. The manufacturer also supplies a sensitivity analysis that retains 4 weekly dosing for denosumab, but assumes a percentage of bisphosphonate patients receive 3 weekly dosing in line with their chemotherapy regime.

Within the denosumab trials intravenous therapy could be withheld due to elevated creatine. This affects the average dose received within the zoledronic acid arm. The clinical study reports provide the subject incidence of IV dose withholding, though it is not clear to the assessment group whether this corresponds to the number of patients having their dose withheld or the number of doses withheld. 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. But on the conservative assumption that the incident patient dose withheld data is equivalent to only one dose being withheld the figures imply the following.

**Table 80 Zoledronic acid withheld during denosumab trials**

| | Breast cancer | Prostate Cancer | Other solid tumours |
|---|---|---|---|
| **N** | [redacted] | [redacted] | [redacted] |
| **N IV Zoledronic acid withheld** | [redacted] | [redacted] | [redacted] |
| **% IV Zoledronic acid withheld** | [redacted] | [redacted] | [redacted] |
| **Average ZA doses** | [redacted] | [redacted] | [redacted] |
| **Total ZA dose exposure** | [redacted] | [redacted] | [redacted] |
| **ZA withheld %** | [redacted] | [redacted] | [redacted] |

The impact of this has not been included within the direct drug and administration costs calculated by the manufacturer.

*SRE costs*

***The STARS costing study***

The STARs costing study is a manufacturer commissioned observational study across the USA, Canada, the UK, Germany, Italy and Spain. This recruited patients with bone metastases secondary to breast cancer, prostate cancer, lung cancer or multiple myeloma who had had an SRE during the previous 90 days. Subjects were followed up for an average of around 18 months.

Health care resource use across a number of different categories was collected: inpatient data, outpatient visits, procedures, emergency room visits, nursing home use and home health visits. The attribution of this resource use to an SRE was apparently at investigator discretion, with no details of the methods for this being reported in the submission.

The health care resource use drawn from the STARs study for the submission is specific to the [redacted] UK patients within the study. The STARs study included multiple-myeloma patients but from the data presented in the electronic copy of the manufacturer model it appears that the [redacted] multiple-myeloma SREs have been excluded from the total [redacted] observed to leave [redacted] SREs split into [redacted] SREs among breast cancer patients, [redacted] among lung cancer patients and [redacted] among prostate cancer patients.

*Trim points and manufacturer costings*

For the derivation of the average inpatient cost per event the manufacturer costings include an allowance for the excess bed days within the NHS reference costs. The manufacturer calculates a weighted average length of stay across elective inpatients, non-elective long stay inpatients and non-elective short stay inpatients for the identified HRGs. This average HRG length of stay is taken as the trim point. If the average length of stay observed within the STARs study exceeds this, the manufacturer costs this excess at the excess bed day rate for the identified HRGs, averaged across elective inpatients and non-elective long stay inpatients.

For instance, the average length of stay across the three HRGs identified for non-vertebral fractures treated as an inpatient is calculated as 7.93 days. Among those treated as inpatients for non-vertebral fracture, the STARs study average length of stay is given as [redacted] days. The manufacturer calculates the excess bed days as [redacted] days minus 7.93 days: [redacted] days which are costed at £217 per day to yield an excess bed day cost of [redacted]. This is added to the weighted average inpatient cost across the three HRGs of [redacted] to yield an overall total cost for non-vertebral fractures treated on an inpatient basis of [redacted].

But the 2011-11 episode trim points for the three identified HRGs[26] are 45 days, 21 days and 19 days respectively. While the average treatment duration within the STARs study will encompass a spread of values it is questionable whether any allowance for excess bed day costs should have been made by the manufacturer.

These considerations around excess bed day trim points applies throughout the manufacturer costings of inpatient stays for the other SREs and AEs.

[26] HD39A, HD39B and HD39C

**Table 81 STARs SRE costing study inpatient data**

| | V Fracture | NV Fracture | Radiation | Surgery | SCC |
|---|---|---|---|---|---|
| **Average IP stays per patient** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Average duration per stay** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Of which assumed within trim point** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Of which assumed excess bed days** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| V Fracture: Vertebral fracture, NV Fracture: Non-vertebral fracture, Radiation: Radiation to the bone, Surgery: Surgery to the bone, SCC: Spinal cord compression | | | | | |

*Radiotherapy to the bone costing*

For reasons that are not clear, to cost radiotherapy planning and administration the manufacturer uses 2008-09 reference costs and indexes these for inflation, rather than using the 2009-10 reference costs which are employed for all the other SREs.

For the planning of radiotherapy the manufacturer includes the HRG codes SC01Z through to SC03Z which seems reasonable. It may be more questionable to have included SC04Z relating to planning multiple phases of complex radiotherapy and SC010Z relating to planning "other" radiotherapy. The weighted average cost across inpatients, day cases, outpatients and "other" settings is applied to all those receiving radiotherapy.

Similarly, for the delivery of radiotherapy the manufacturer includes the HRG codes SC21Z through to SC24Z, all of which relate to delivering a single fraction of radiotherapy. Again, it may be more questionable to have included SC29Z relating to the delivery of "other" radiotherapy, the unit costs of this typically being somewhat higher than that of the HRGs specifically relating to delivering a single fraction of radiotherapy. The weighted average cost across inpatients, day cases, outpatients and "other" settings is multiplied by the average number of [redacted] fractions drawn from STARs study.

*Base case SRE costs*

The STARs based costing results in the following cost estimates.

**Table 82 STARs based costing results**

| | V Fracture | NV Fracture | Radiation | Surgery | SCC |
|---|---|---|---|---|---|
| **N** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Inpatient Cost** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Outpatient Cost** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Emergency Care Cost** | | [redacted] | | | [redacted] |
| **Home health visits** | | [redacted] | | [redacted] | [redacted] |
| **Procedures** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Total STARs cost** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Base case cost applied** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

V Fracture: Vertebral fracture, NV Fracture: Non-vertebral fracture, Radiation: Radiation to the bone, Surgery: Surgery to the bone, SCC: Spinal cord compression

Vertebral fracture is something of an outlier within these costings, with quite significant costs being associated with outpatient visits and outpatient procedures. Possibly due to questionable reliability of the resource use around this with only [redacted] having been observed, coupled with expert opinion that vertebral fractures are typically asymptomatic to the extent of not being treated, the manufacturer applies no cost for vertebral fractures in the base case.

*AE costs*

As already noted, the cost of treating hypercalcaemia £4,579 [£3,791 2004] as drawn from the Ross HTA Monograph is used for the base case.

For hypocalcaemia the manufacturer assumes that this will require one haematology consultant led outpatient appointment, one intravenous calcium injection, and two follow up visits. Each visit is associated with a blood test, to yield a total cost per event of £443.

For the other adverse events the manufacturer assumes that all will be treated as inpatients and simply averages the inpatient cost over a range of HRGs:

- osteonecrosis of the jaw HRGs: CZ16 minor maxillo facial procedures, CZ17 intermediate maxillo facial procedures, CZ18 major maxillo facial procedures, and CZ19 complex maxillo facial procedures, to arrive at an average cost of £2,465
- renal toxicity HRGs: all LA07 acute kidney injury and all LA08 chronic kidney disease but not LA09 general renal disorders, to arrive at an average £1,681

- skin infections HRG: only JD04B minor skin disorders category 3 with Intermediate CC at £1,440

### *11.2.5 Quality of Life*

EQ-5D data was administered during the denosumab trials, and this data set is probably the best source of HRQoL data for estimating the impact of SREs upon patient quality of life for the purposes of economic modelling. As explored in greater detail below, the manufacturer has undertaken an involved analysis of this data. Prior to exploring the analysis presented by the manufacturer two quite large caveats are in order:

- At the stakeholder briefing meeting, the manufacturer undertook to supply the full EQ-5D data analysis report as an appendix to the NICE submission. This report has not been supplied.
- 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.

The key assumption underlying the functional form chosen by the manufacturer is that only SREs and AEs related to metastatic bone disease and its treatment affect deviations from the baseline HrQoL. In the context of the underlying condition(s) being cancer with the possibility of progression, the development of metastatic disease in areas other than the bone and the relatively short anticipated average survival this appears to be a very strong assumption. 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[199] reference summarised in the quality of life review above. Not considering progression within the modelling of utility is surprising.

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.

Note that the manufacturer's submission makes the assumption that utility 6 months prior to the diagnosis of an SRE is at the relevant baseline value, SRE naïve or SRE experienced, and that 6 months subsequent to the diagnosis of the SRE returns to the baseline SRE experienced level. Given this, the overall QALY impact of an SRE is in effect calculated as the area between the curves. To illustrate this within the graphs of the calculation of disutility for SRE niave and experienced patients in the submission the manufacturer, the anticipated impacts of radiation to the bone for a breast cancer

patient. The figure below replicates this for the 11 months centred around radiation to the bone at T0 for an SRE experienced breast cancer patient, where the vertical axis measures the HRQoL and the horizontal axis is in time in months.

This is perhaps the neatest evolution of HRQoL due to an SRE within the manufacturer analysis. It can be taken as an argument in favour of estimating the QALY impact of radiation to the bone as the area between the SRE experienced straight line for those not experiencing and SRE and the curve for the evolution of HRQoL associated with radiation to the bone of an SRE experienced patient.

But not all the curves are quite so tidy, as shown in full in Appendix 13. Cherry picking to a similar degree but in the opposite direction as the manufacturer, the evolution of HRQoL due to vertebral fracture within the other solid tumours group of cancer patients for an SRE experienced patient is graphed below.

[redacted]

It is not obvious that the HRQoL impact of the vertebral fracture should be taken as far back as 5 months prior to its diagnosis. The dip at four months prior to diagnosis of vertebral fracture is not maintained and might be better discarded as an effect. It is also possibly questionable to include the estimated effects for the full five months subsequent to the diagnosis of the vertebral fracture. From the above, the argument could be made that the HRQoL impact of vertebral fractures is limited to the two month subsequent to T0.

These considerations outlined may apply in the opposite direction for the evolution of HRQoL due to spinal cord compression. While the picture varies across the cancers there is some similarity in terms of a possibly permanent effect, as would be anticipated given that a proportion of patients will have some degree of paralysis.

[redacted]

In this instance it can be argued that only evaluating the QALY impact of spinal cord compression for the five months subsequent to diagnosis of spinal cord compression may have underestimated the HRQoL impact of spinal cord compression. The HRQoL decrements estimated for the months subsequent to spinal cord compression for the SRE experienced patient are presented below, together with the baseline HRQoL value for SRE naïve and SRE experienced patients for ease of reference.

**Table 83 Spinal cord compression HRQoL decrement estimates post diagnosis**

| | **Breast cancer** | **Prostate cancer** | **Other solid tumours** |
|---|---|---|---|
| **SRE naive baseline HRQoL** | [redacted] | [redacted] | [redacted] |
| **SRE exp. baseline HRQoL** | [redacted] | [redacted] | [redacted] |
| **Permanent loss from 1st SRE** | [redacted] | [redacted] | [redacted] |
| **SCC HRQoL decrements** | | | |
| **1st month post diagnosis** | [redacted] | [redacted] | [redacted] |
| **2nd month post diagnosis** | [redacted] | [redacted] | [redacted] |
| **3rd month post diagnosis** | [redacted] | [redacted] | [redacted] |
| **4th month post diagnosis** | [redacted] | [redacted] | [redacted] |

| | | | |
|---|---|---|---|
| **5th month post diagnosis** | [redacted] | [redacted] | [redacted] |
| **Mean decrement post diagnosis** | [redacted] | [redacted] | [redacted] |

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.

**Table 84 SRE QALY impacts: SRE naïve and SRE experienced**

| | Breast cancer | | Prostate cancer | | Other solid tumours | |
|---|---|---|---|---|---|---|
| | SRE naive | SRE exp | SRE naive | SRE exp | SRE naive | SRE exp |
| **Vertebral fracture** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Non-vertebral fracture** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Radiation to the bone** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Surgery to the bone** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Spinal cord compression** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

In the main, however, based upon a fairly crude assessment of the central values derived and the graphs of the evolution of HRQoL over time as in appendix 13, the manufacturer analysis of the EQ-5D data does not appear to have arrived at unreasonable estimates for the impacts of SREs. But this retains the caveat that no detail of the EQ-5D study in terms of the alternative functional forms that were tested has been provided by the manufacturer. 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). 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.

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 5$^{th}$ and 4$^{th}$ 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 4$^{th}$ and 5$^{th}$ month subsequent to the SRE. This may have quite a large impactupon modelling results, given the overall survival curves and the evolution of SRE utility decrements.

The manufacturer model appears to correctly adjust the post SRE HRQoL decrements for those dying in the 5 months subsequent to an event in order not to project SRE HRQoL impacts beyond death.

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.

Within the model cohort flow in the cycle immediately subsequent to the SRE at T(0) the patient is reclassified as an SRE experienced patient with the associated SRE experienced HRQoL also including the SRE experienced parameter. This may have double counted the impact of the SRE in that the decrement for months 1 to 5 subsequent to the SRE. As an illustration, the evolution of HRQoL for the SRE naïve breast cancer patient experiencing her first SRE as radiation to the bone is outlined below.

The SRE naïve patient experiences a step change in HRQoL when the first SRE is experienced. The QALY decrement associated with the SRE should be calculated as the area between the upper straight line and the lower curve, these extending to the right until death. It seems possible that within this the manufacturer model has double counted the dashed area. This again may have quite a large impact upon results.

The HRQoL impact of an adverse event draws on the same EQ-5D data as that used for estimating the HRQoL impact of SREs. A unified overall model is not presented and the data is analysed separately for SREs and for AEs.

**Table 85 SAE average duration and QALY decrements**

| Adverse Event | Breast Cancer | | Prostate Cancer | | Other Solid Tumours | |
|---|---|---|---|---|---|---|
| | Av. Days | Decrement | Av. Days | Decrement | Av. Days | Decrement |
| **ONJ** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Renal toxicity** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Hypercalcaemia** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Hypocalcaemia** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Skin Infection** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

The assumed duration of HRQoL impacts is lifetime for ONJ and renal toxicity, while the duration of HRQoL impacts from hypercalcaemia, hypocalcaemia and skin infections is as recorded within the individual patient level data.

### *11.2.6 Manufacturer modelling conformity to NICE reference case*

The manufacturer model broadly conforms to the NICE reference case as summarised below.

**Table 86 Comparison with NICE reference case**

| Attribute | Reference case and TA Methods guidance | Does the *de novo* economic evaluation match the reference case |
|---|---|---|
| **Comparator(s)** | Therapies routinely used in the NHS, including technologies regarded as current best practice | Partial.<br><br>Given the NICE breast cancer guideline, assessing denosumab only compared to bisphosphonates for the main analysis is reasonable. But this ignores the patient group contraindicated to bisphosphonates, for whom BSC would have been the appropriate comparator.<br><br>For both prostate and lung cancer the manufacturer splits the patient groups into SRE naive and SRE experienced at baseline. For SRE naïve patients denosumab is assessed against BSC which is appropriate. |

| | | |
|---|---|---|
| | | SRE experience is taken to be a close proxy for uncontrolled pain despite use of conventional analgesics. This enables the manufacturer to model denosumab against bisphosphonates for these patients. The evidence presented by the manufacturer that these patients are on ongoing bisphosphonate use in the UK is not clear cut. There is also no consideration of those contraindicated to bisphosphonate use. |
| **Patient group** | As per NICE scope | Yes. |
| **Perspective costs** | NHS and PSS | Yes. |
| **Perspective benefits** | All health effects | Yes. |
| **Form of evaluation** | Cost-effectiveness analysis | Yes. Cost utility analyses. |
| **Time horizon** | Sufficient to capture differences in costs/outcomes | Yes. 10 years which is in effect, lifetime. |
| **Synthesis of evidence on outcomes** | Systematic review | Yes. A network meta-analysis is undertaken. But note that this differs from the AG NMA in part due to the studies that are included. |
| **Outcome measure** | Quality adjusted life years | Yes. |
| **Health states for QALY** | Using a standardised validated instrument | Yes. Drawn from trial based EQ-5D data. |
| **Benefit valuation** | TTO or standard gamble | Yes. EQ-5D converted to utilities using the UK social tariff. |
| **Source of preference data for valuation of changes in HRQL** | Representative sample of the public | Yes. The UK social tariff. |
| **Discount rate** | An annual rate of 3.5% on both costs and health effects | Yes. |
| **Equity** | An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit | Yes. |
| **Probabilistic modelling** | Probabilistic modelling | Yes. |
| **Sensitivity analysis** | | A range of univariate sensitivity analyses are presented. |

### *11.2.7 Manufacturer base case results*

What follows are the manufacturer reported estimates for the cost effectiveness of denosumab compared to the primary comparator, plus additional pairwise comparisons where the NMA provides effectiveness estimates for other bisphosphonates.

Unfortunately, the manufacturer has not reported results relative to BSC for those contraindicated to bisphosphonates.

*Breast cancer: All patients*

**Table 87 Manufacturer disaggregate base case results for breast cancer all patients**

| | **Breast cancer: All Patients** | | | |
|---|---|---|---|---|
| | **Denos.** | **Zol. acid** | **Diso** | **Iban** |
| **LY (undisc)** | 3.45 | 3.45 | 3.45 | 3.45 |
| **LY (disc)** | 3.16 | 3.16 | 3.16 | 3.16 |
| **SREs** | 2.13 | 2.34 | 2.47 | 2.30 |
| **QALYs** | 1.912 | 1.904 | 1.898 | 1.907 |
| **Net QALYs vs Denos.** | 0.000 | -0.007 | -0.013 | -0.005 |
| **Costs** | | | | |
| **Treatment** | | | | |
| **Ex PAS** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Inc PAS** | [redacted] | | | |
| **SREs** | £2,932 | £3,241 | £3,435 | £3,199 |
| **AEs** | £93 | £137 | £317 | £37 |
| **Death** | £4,356 | £4,356 | £4,356 | £4,356 |
| **Total Costs** | | | | |
| **Ex PAS** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Inc PAS** | [redacted] | | | |
| **Net ex PAS vs Denos.** | £0 | -£1,483 | £1,487 | -£72 |
| **Net inc PAS vs Denos.** | £0 | £483 | £3,453 | £1,895 |

The base case results are that denosumab prevents on average around 0.21 SREs compared to zoledronic acid. Among those contraindicated to bisphosphonates, denosumab is anticipated to prevent on average around 0.91 SREs compared to BSC. These yield a gain from denosumab of 0.007 QALYs compared to zoledronic acid. Excluding the PAS, the net overall cost increase from denosumab is £1,483 compared to zoledronic acid. Including the PAS, denosumab is estimated to

yield cost savings of £483 compared to zoledronic acid. This results in the following cost effectiveness estimates for denosumab within the pairwise comparisons.

**Table 88 Manufacturer base case cost effectiveness results for breast cancer all patients**

| | Costs (£) | QALYs | ΔCosts (£) | ΔQALYs | ICER |
|---|---|---|---|---|---|
| **Denosumab with PAS** | [redacted] | 1.912 | | | |
| **Zoledronic Acid with PAS** | [redacted] | 1.904 | £1,484<br>-£483 | 0.007 | £203,387<br>Denosumab Dominant |
| **Disodium pamidronate with PAS** | [redacted] | 1.898 | -£1,486<br>-£3,453 | 0.013 | Denosumab Dominant<br>Denosumab Dominant |
| **Ibandronic acid with PAS** | [redacted] | 1.907 | £72<br>-£1,895 | 0.005 | £13,835<br>Denosumab Dominant |

Without the PAS, the cost effectiveness of denosumab versus zoledronic acid is estimated as £203,387 per QALY. The additional benefit of 0.007 QALYs does not warrant the additional cost of £1,483. Probabilistic modelling undertaken by the manufacturer results in an identical central estimate of a 0.007 QALY gain over zoledronic acid for a similar average additional cost of £1,490.

With the PAS, denosumab is estimated to be cost saving relative to zoledronic acid. Given the small additional QALY gain, this results in denosumab dominating zoledronic acid. Probabilistic modelling undertaken by the manufacturer results in the same central estimate of QALYs gained with a similar average cost saving of £481 from denosumab compared to zoledronic acid.

Prostate cancer: SRE experienced

**Table 89 Manufacturer disaggregate base case results for prostate cancer SRE experienced**

| | SRE experienced patients (26%) | |
|---|---|---|
| | **Denos.** | **Zol. Acid** |
| **LY (undisc)** | 2.17 | 2.17 |
| **LY (disc)** | 2.04 | 2.04 |
| **SREs** | 1.98 | 2.12 |
| **QALYs** | 1.089 | 1.083 |
| **Net QALYs vs Denos.** | | -0.006 |
| **Costs** | | |
| **Treatment** | | |
| **Ex PAS** | [redacted] | [redacted] |
| **Inc PAS** | [redacted] | |
| **SREs** | £2,810 | £3,010 |
| **AEs** | £165 | £125 |
| **Death** | £4,625 | £4,625 |
| **Total Costs** | | |
| **Ex PAS** | [redacted] | [redacted] |
| **Inc PAS** | [redacted] | |
| **Net ex PAS vs Denos.** | | -£922 |
| **Net inc PAS vs Denos.** | | £281 |

The QALY gains anticipated from denosumab over zoledronic acid are slightly smaller than but similar to those within breast cancer at 0.006 QALYs with the lower survival limiting the potential for patients' gains. Excluding the PAS the incremental cost of denosumab is estimated as £922 versus zoledronic acid, but with the PAS denosumab results in cost savings of £281 compared to zoledronic acid. This results in the following cost effectiveness estimates.

**Table 90 Manufacturer base case cost effectiveness results for prostate cancer SRE experienced**

| | Costs (£) | QALYs | ΔCosts (£) | ΔQALYs | ICER |
|---|---|---|---|---|---|
| **Denosumab with PAS** | [redacted] | 1.089 | | | |
| **Zoledronic Acid with PAS** | [redacted] | 1.083 | £922<br>-£281 | 0.006 | £157,276<br>Denosumab Dominant |

Without the PAS, the cost effectiveness of denosumab versus zoledronic acid is estimated as £157,276 per QALY. Probabilistic modelling undertaken by the manufacturer suggests the same average gain of 0.006 QALYs from denosumab over zoledronic acid for a similar average cost of £918. With the PAS, denosumab is estimated to result in a cost saving of £281 compared to zoledronic acid and as a consequence, given the small gain of 0.006 QALYs, is estimated to dominate zoledronic acid. Probabilistic modelling undertaken by the manufacturer indicates the same average gain from denosumab over zoledronic acid of 0.006 QALYs with an additional average cost saving of £286.

*Prostate cancer: SRE naive*

For the SRE naïve patients, who made up 74% of the denosumab trial population, the base case cost effectiveness results are summarised below.

**Table 91 Manufacturer base case cost effectiveness results for prostate cancer SRE naive inc. PAS**

| | Costs (£) | QALYs | ΔCosts (£) | ΔQALYs | ICER |
|---|---|---|---|---|---|
| **Denosumab** | [redacted] | 1.189 | | | |
| **with PAS** | [redacted] | | | | |
| **BSC** | [redacted] | 1.150 | £3,993 | 0.039 | £102,067 |
| **with PAS** | | | £2,790 | | £71,320 |

Without the PAS, denosumab is estimated to have a cost effectiveness compared to BSC of £102,067 per QALY. With the PAS, the cost effectiveness estimate falls but only to £71,320 per QALY which is also well above normal cost effectiveness thresholds. Probabilistic modelling by the manufacturer is in line with this, with denosumab yielding a central estimate of 0.039 QALYs over BSC but at an average net cost of £2,776.

*Other solid tumours: SRE experienced*

*Table 92 Manufacturer disaggregate base case results for OST SRE experienced*

| | **SRE experienced patients (48%)** | | |
|---|---|---|---|
| | **Denos.** | **Zol. Acid** | **Disod. Pam.** |
| **LY (undisc)** | 1.76 | 1.76 | 1.76 |
| **LY (disc)** | 1.64 | 1.64 | 1.64 |
| **SREs** | 1.37 | 1.46 | 1.47 |
| **QALYs** | 0.765 | 0.761 | 0.759 |
| **Net vs Denosumab** | | -0.004 | -0.006 |
| **Costs** | | | |
| **Treatment** | | | |
| **Ex PAS** | [redacted] | [redacted] | [redacted] |
| **Inc PAS** | [redacted] | | |
| **SREs** | £2,556 | £2,714 | £2,754 |
| **AEs** | £57 | £57 | £183 |
| **Death** | £4,612 | £4,612 | £4,612 |
| **Total Costs** | | | |
| **Ex PAS** | [redacted] | [redacted] | [redacted] |
| **Inc PAS** | [redacted] | | |
| **Net ex PAS vs Denos.** | | -£757 | £2,118 |
| **Net inc PAS vs Denos.** | | £43 | £2,918 |

The QALY gains anticipated from denosumab are smaller than those estimated for the previous analyses: 0.004 QALYs compared to zoledronic acid. Excluding the PAS the incremental cost of denosumab is estimated as £757 versus zoledronic acid but sees cost savings of £2,118 versus pamidronate.With the PAS denosumab results in cost savings of £43 compared to zoledronic acid and the net saving relative to pamidronate increase to £2,918. This results in the following cost effectiveness estimates.

**Table 93 Manufacturer base case cost effectiveness results for OST cancer SRE experienced**

| | Costs (£) | QALYs | ΔCosts (£) | ΔQALYs | ICER |
|---|---|---|---|---|---|
| **Denosumab** | [redacted] | 0.765 | | | |
| **with PAS** | [redacted] | | | | |
| **Zoledronic Acid** | [redacted] | 0.761 | £757 | 0.004 | £205,580 |
| **with PAS** | | | -£43 | | Denosumab Dominant |
| **Disodium pamidronate** | [redacted] | 0.759 | -£2,118 | 0.006 | Denosumab Dominant |
| **with PAS** | | | -£2,918 | | Denosumab Dominant |

Without the PAS, the cost effectiveness of denosumab versus zoledronic acid is estimated as £205,580 per QALY. Probabilistic modelling undertaken by the manufacturer paints a similar picture at central estimates, with an average gain from denosumab over zoledronic acid of 0.004 QALYs at an average net cost of £749.

With the PAS, denosumab is estimated to result in a cost saving of £43 compared to zoledronic acid and given the small gain of 0.004 QALYs to dominate zoledronic acid. Probabilistic modelling undertaken by the manufacturer again paints a similar picture as the deterministic modelling, with an average gain from denosumab over zoledronic acid of 0.004 QALYs with a small cost saving of £45.

*Other solid tumours: SRE naive*

For the SRE naïve patients, who made up 52% of the denosumab trial population, the base case cost effectiveness results are summarised below.

**Table 94 Manufacturer base case cost effectiveness results for OST cancer SRE naive inc. PAS**

| | Costs (£) | QALYs | ΔCosts (£) | ΔQALYs | ICER |
|---|---|---|---|---|---|
| **Denosumab** | [redacted] | 0.803 | | | |
| **with PAS** | [redacted] | | | | |
| **BSC** | [redacted] | 0.782 | £2,530 | 0.021 | £122,499 |
| **with PAS** | | | £1,730 | | £83,763 |

For the primary comparator of BSC, even with the PAS the resulting cost effectiveness estimate for denosumab of £83,763 per QALY is again well above normal cost effectiveness thresholds. Probabilistic modelling is in line with this, with denosumab yielding an average 0.021 QALYs over BSC but at an average net cost of £1,724.

### *11.2.8 Manufacturer structural and sensitivity analyses*

The manufacturer undertakes a range sensitivity analyses that apply:

- time horizons of 2 and 5 years;
- no 21 day window for the definition of SREs;
- costs to vertebral fracture as estimated from the STARs costing exercise,
- the SRE costs as estimated from NHS reference cost admission rates,
- the manufacturer commissioned TTO utilities and the Weinfurt utilities,[129]
- starting ages of 50 and 65,
- a balance between 3 weekly and 4 weekly dosing for IV bisphosphonate administrations,
- oral administration for ibandronic acid,
- community administration for denosumab,
- no discontinuations and a constant 0.025 discontinuation rate per cycle for all treatments; and,
- sensitivity analyses around the discount rates.

Many of these sensitivity analyses have relatively little impact upon the outcomes of the modelling. The full sensitivity analyses presented by the manufacturer for the with PAS scenario are included in appendix 14 of this report.

For the breast cancer modelling across all patients, without the PAS results are reasonably sensitive to:

- The time horizon adopted, which if only 2 years worsens the ICER for denosumab compared to zoledronic acid from £203k per QALY to £254k per QALY, and compared to zoledronic acid from £14k per QALY to £149k per QALY.
- The source of utilities, with the TTO values increasing the net gain from denosumab by around 20% with parallel effects upon the ICERs, while the Weinfurt utilities decrease the net gain from denosumab by a slightly smaller percentage.
- Ibandronic acid being administered orally, which worsens the ICER for denosumab compared to it to £387k per QALY.
- The frequency of dosing for the IV bisphosphonates as would be anticipated, reducing the net cost of denosumab over zoledronic acid by around 20% and causing the ICER to fall to £161k per QALY. For the other comparisons, including some 3 weekly IV dosing is sufficient for denosumab to be cost saving and so dominant.
- The discontinuation rates assumed, with a zero discontinuation rate increasing the net lifetime costs from denosumab use. This mainly affects the comparison with ibandronic acid where the ICER worsens to [redacted] per QALY.

With the PAS, similar effects are observed among breast cancer patients in terms of the changes to the net QALYs and net costs but the sensitivity analyses still result in denosumab being estimated to be cost saving and to confer small QALY gains, and so dominate the other treatments. Only oral ibandronic acid stands out with a small net cost from denosumab use of [redacted], resulting in a cost effectiveness estimate of £387 per QALY.

For SRE experienced prostate cancer patients, without the PAS results are reasonably sensitive to:

- Excluding the 21 day window from the identification of SREs, with this improving the ICER for denosumab compared to zoledronic acid from £157k per QALY to £89k per QALY.
- Basing the utility estimates upon the Weinfurt reference, which worsens the ICER to £384k per QALY.
- The frequency of dosing for the IV bisphosphonates, reducing the net cost of denosumab over zoledronic acid and causing the ICER to fall to £125k per QALY
- Community administration of denosumab, causing the ICER to fall to [redacted] per QALY.

With the PAS, as for the breast cancer modelling similar effects are observed in terms of the changes to the net QALYs and net costs but the sensitivity analyses still result in denosumab being estimated to be cost saving and to confer small QALY gains, and so dominate zoledronic acid.

For SRE naive prostate cancer patients, even with the PAS the sensitivity analyses result in ICERs in the range £50k per QALY to £355k per QALY, which are outside the range usually considered to be cost effective.

For SRE experienced other solid tumour patients, for the comparison with zoledronic acid the cost effectiveness of denosumab without the PAS is reasonably sensitive to:

- Excluding the 21 day window from the identification of SREs, with this improving the ICER for denosumab compared to zoledronic acid from £206k per QALY to £144k per QALY.
- Basing the utility estimates upon the Weinfurt reference, which worsens the ICER to £420k per QALY.
- The frequency of dosing for the IV bisphosphonates, reducing the net cost of denosumab over zoledronic acid and causing the ICER to fall to £176k per QALY.
- Community administration of denosumab, causing the ICER to fall to [redacted] per QALY.
- Zero discontinuations across treatments which improves the ICER to [redacted] per QALY

With the PAS, as for the modelling of prostate cancer and breast cancer similar effects are observed in terms of the changes to the net QALYs and net costs but the sensitivity analyses still result in

denosumab being estimated to be cost saving and to confer small QALY gains, and so dominate zoledronic acid.

For SRE naive other solid tumour patients, even with the PAS the sensitivity analyses result in ICERs in the range £70k per QALY to £320k per QALY and would not typically be considered cost effective.

### *11.2.9 Assessment Group critique of the manufacturer model and results*

The manufacturer case is broadly that while the average patient benefits from the reduced number of SREs is not large, [redacted]

But for patients for whom zoledronic acid is not indicated, the manufacturer accepts that even with the PAS the relatively small patient gains do not justify the additional cost of denosumab. Manufacturer cost effectiveness estimates for denosumab compared to BSC are typically closer to £100k per QALY than £50k per QALY, even with the PAS.

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.

The estimation of utility decrements from the trials' EQ-5D data is at first pass impressive, but the complete lack of detail about the alternative functional forms that have been tested raises concerns. It also seems surprising that other aspects of the underlying cancers were not included as covariates. With this caveat and as there is no consideration of progression within the utility data, the general model structure employed by the manufacturer appears reasonable. It is also in line with the NICE reference case.

The manufacturer implementation of the utility data within the model may have two errors within it. If so, these are likely to pull in opposite directions. The model appears to attempt to correct so as not to project benefits prior to the start of therapy. But it appears that this may cut off the patient benefits in

the 5 months following an SRE occurring in the first cycle of the model, in the 4 months following an SRE occurring in the second cycle of the model, etc.. Pulling in the opposite direction, it also appears that the SRE decrement among SRE naïve patients is measured from the SRE naïve baseline HRQoL for the five months subsequent to an SRE, but the patient is modelled as also stepping down to the SRE experienced HRQoL for this period and beyond. This may double count the impact of first SREs in the five months subsequent to their incidence.

## 11.3 Independent economic assessment

### *11.3.1 Methods*

Prior to any cost effectiveness modelling, some basic considerations should be borne in mind. Within the literature there are two broad strands of cost effectiveness assessments: the straightforward assessments of within trial costs and benefits; and, the more complicated modelling of costs and benefits with extrapolation to death, this latter also permitting other comparators to be included than just those studied within the trial. The more complicated modelling, including that of the Amgen submission, typically treats metastatic bone disease as a chronic condition. This gives rise to an SRE rate in one arm under consideration, with comparator treatments affecting this rate. There are additional considerations around distinguishing between the time to first SRE for SRE naïve patients, compared to the rate of subsequent SREs for SRE experienced patients. Almost by definition, extrapolation beyond the trial is likely to alter the patient balance towards SRE experienced patients as SRE naïve patients experience SREs. Cost effectiveness may differ between SRE naïve patients and SRE experienced patients.

But even in the light of this, given that the condition is typically modelled as being chronic and stable through to death with discontinuations immediately leading to the BSC risk of an event, there is an argument for a simple economic assessment of the within trial outcomes prior to any more sophisticated cost utility economic modelling and extrapolation.

The more simple minded assessment of the within trial considers the economic implications of:

- the average number of treatments in each arm of the trials;
- the average number of SREs per patient in each arm of the trials;
- the average number of SAEs per patient in each arm of the trials; and
- the average months on study within each arm and how this may condition the above.

Unfortunately, the AG does not have access to sufficiently disaggregate data to present this analysis for the SRE naïve and SRE experienced subgroups.

Other than the paper by Xie and colleagues[186] the cost effectiveness literature has not explicitly modelled progression or considered any explicit stopping rule. There are three main reasons why disease progression may affect cost effectiveness:

- the rate of SREs may change at progression;
- a proportion of patients discontinue therapy at progression, which may differ between treatments; and,
- the general patient quality of life and the quality of life impacts from SREs may change at progression.

Modelling the above would require the progression free survival curves for each cancer, which are available from the denosumab CSRs. But it would also require the time to first SRE and the rate or time to subsequent SREs within the zoledronic acid arm to be split by those without disease progression and those with progression. This data is not readily available. There would also be the question of whether the relative effect for the other comparators would remain constant at progression. The additional concern about how to model the quality of life impacts of SREs among progression free patients and patients with progression is also not readily addressable given the quality of life estimates within the literature and the Amgen submission.

The assessment group views the structure of the manufacturer's model as a reasonable basis for the estimation of cost effectiveness. There is no suggestion that treatments affect the rate of progression or overall survival. If progression changes the rate of SREs, this can be explored by sensitivity analyses that change the rate of SREs from a given cycle in the model onwards. Quality of life declining towards the end of life can be explored through a structural sensitivity analysis that applies the EQ-5D utilities of van den Hout and colleagues.[199]

In the light of this, the assessment group has rebuilt the model using the same overall structure as the manufacturer model, the main adjustments within this being to the treatment of utilities in order to adjust for not projecting benefits to before the start of treatment, and to measure any utility decrements subsequent to an SRE from the SRE experienced baseline utility. In the absence of other data, the average utility decrement for SREs within lung cancer has been assumed to be the same as within the other solid tumours including lung cancer trial.

The base case of the modelling applies the results of the AG NMA. Additional structural elements added to the model are the facility for: spinal cord compression to have a sustained HRQoL impact beyond 5 months from diagnosis, and, a decay in quality of life in the final year, as estimated by van den Hout.[199] These are only applied as sensitivity analyses to the base case.

Given the AG NMA results, cost effectiveness results are presented for four cancer groups:

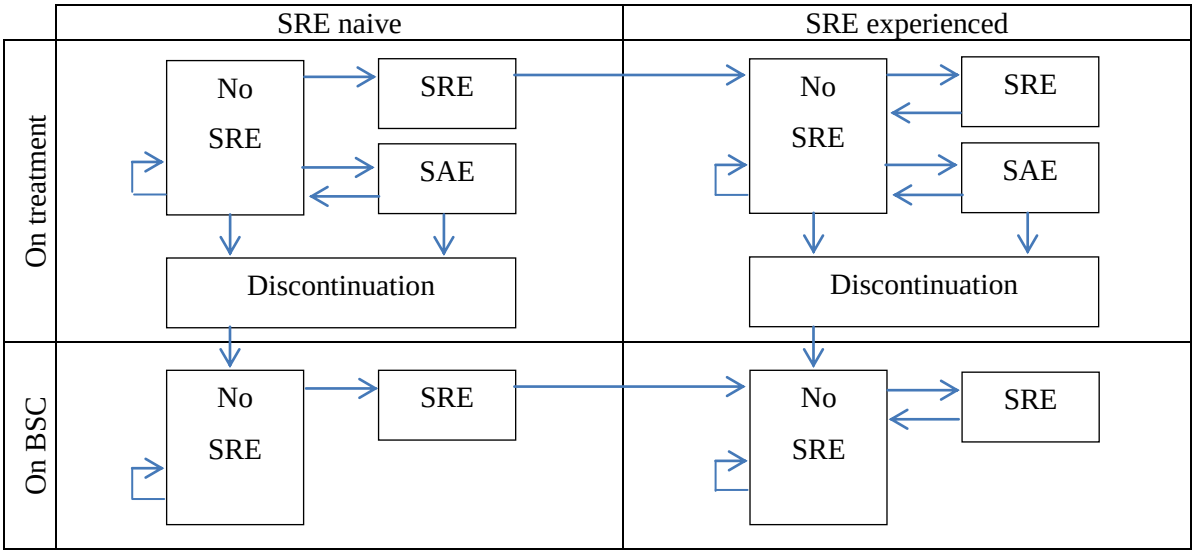
- breast cancer;
- prostate cancer;
- other solid tumours including lung cancer (OST+Lung);
- lung cancer.

These are further subdivided into;

- All patients;
- SRE naïve patients; and,
- SRE experienced patients.

The model structure can be presented diagramatically:

**Figure 12 Cost utility model structure**




With the following analyses being presented, and compared with those of the manufacturer. Within the following: pooled relates to the HRs and RRs of an SRE being drawn from the trial data pooled across SRE naïve and SRE experienced patients, while specific relates to the HRs and RRs of an SRE being specific to whether it is an SRE naïve patient or an SRE experienced patient being modelled.

**Table 95 Principle cost utility analyses presented**

| | Breast cancer | | Prostate cancer | | OST + Lung | | Lung cancer | |
|---|---|---|---|---|---|---|---|---|
| **SRE RR and HR** | **Pooled** | **Specific** | **Pooled** | **Specific** | **Pooled** | **Specific** | **Pooled** | **Specific** |
| **Manufacturer** | | | | | | | | |
| All patients | ✓ | × | × | × | × | × | × | × |
| SRE naive | × | × | ✓ | × | ✓ | × | × | × |
| SRE experienced | × | × | ✓ | × | ✓ | × | × | × |
| AG | | | | | | | | |
| All patients | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | × |
| SRE naive | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | × |
| SRE experienced | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | × |

For the above, the cost utility analyses that employ the pooled HRs and RRs are presented as the base case. A range of univariate sensitivity analyses around these estimates are then presented in summary format.

The AG views the structural sensitivity analyses that employ the SRE naïve and SRE experienced specific HRs and RRs as sufficiently important for the full results of their impacts upon the base case to be reported. This is complicated by the results of the AG NMA being pooled across all patients; i.e. not being specific to SRE naïve or SRE experienced patients. In the light of this and the manufacturer's summary of subgroup by prior SRE history for time to first and time to first-and-subsequent on-study SRE, the structural sensitivity analyses apply the SRE specific head-to-head clinical effectiveness estimates for the effectiveness of denosumab compared to zoledronic acid, while retaining the results of the AG NMA for the other comparator(s). This distinction is not available for the modelling of lung cancer.

*Clinical parameters and effectiveness data for the modelling*

The simplistic analysis of CSR data draws the rates of SREs and SAEs from the CSRs, the manufacturer model and the manufacturer submission, with cross checks between the two sources.

The cost utility modelling draws heavily upon the manufacturer model.

- Hazard ratios and relative risks of SREs

The base cases apply the results of the AG NMA. The results of the manufacturer NMA are applied as sensitivity analyses. The structural sensitivity analyses applying the SRE naïve and SRE experienced HRs and RRs apply those summarised in table 76 above.

- Survival

Overall survival is mainly drawn from the manufacturer model and as summarised in table 71 above. Overall survival for lung cancer is drawn from the estimate for zoledronic acid presented within Joshi and colleagues[182] using a weibull extrapolation with survival at a given day being determined by:
S(t) =exp (-0.00181455*t^1.06762733).

- Time to first SRE and rate of subsequent SREs

Due to the manufacturer having access to individual patient level data restricted to the SRE naïve patient subgroup, the base cases for breast, prostate, and other solid tumours including lung cancer apply the time to first SRE curves presented within the manufacturer submission and summarised in table 74 above. These are not available for lung cancer, and the base cases apply the AG estimate for this as summarised below. The additional AG estimates for the time to first SRE for zoledronic acid are applied as sensitivity analyses within the modelling.

**Table 96 AG time to first SRE for zoledronic acid Mean Square Error estimates**

| | **SRE naive** | | **All patients** | | | |
|---|---|---|---|---|---|---|
| | **Breast** | **Prostate** | **Breast** | **Prostate** | **OST+Lung** | **Lung** |
| **Weibull** | 0.000249 | 0.000115 | 0.000351 | 0.000148 | 0.000335 | 0.000128 |
| **Log-logistic** | 0.000225 | 0.000106 | 0.000272 | 0.000081 | 0.000380 | 0.000092 |
| **Lognormal** | **0.000205** | 0.000114 | **0.000213** | **0.000074** | 0.000383 | **0.000088** |
| **Gamma** | 0.000242 | **0.000105** | 0.000294 | 0.000083 | **0.000325** | 0.000111 |

**Table 97 AG time to first SRE for zoledronic acid parameter estimates**

| **SRE Naive** | **Distribution** | **Intercept** | **Scale** | **Shape** |
|---|---|---|---|---|
| Breast | Lognormal | 3.62 | 1.84 | |
| Prostate | Gamma | 3.51 | 1.28 | 0.8 |
| **All patients** | **Distribution** | **Intercept** | **Scale** | **Shape** |
| Breast | Lognormal | 3.33 | 1.97 | |
| Prostate | Lognormal | 2.85 | 1.48 | |
| OST + Lung | Gamma | 3.55 | 1.54 | 0.82 |
| Lung | Lognormal | 2.62 | 2.73 | |

For similar arguments, the base cases for breast, prostate, and other solid tumours including lung cancer apply a cycle rate of SREs within the zoledronic acid arm as estimated by the manufacturer from trial data specific to the SRE experienced subgroup. For lung cancer the AG has, in the absence

of other data, estimated cycle rates based upon the pooled data across all patients; i.e. not specific to the SRE experienced subgroup.

**Table 98 AG subsequent SRE rates for zoledronic acid functional form**

| Zoledronic arms | Prior SRE | | | All patients |
|---|---|---|---|---|
| (with 21-day window) | Breast | Prostate | OST+Lung | Lung |
| Sample size | [redacted] | [redacted] | [redacted] | [redacted] |
| Length of study (months) | [redacted] | [redacted] | [redacted] | [redacted] |
| Length of study (years) | [redacted] | [redacted] | [redacted] | [redacted] |
| Overall survival hazard rate (estimate) | [redacted] | [redacted] | [redacted] | [redacted] |
| Patient years of exposure | [redacted] | [redacted] | [redacted] | [redacted] |
| Cumulative mean rate at end of study | [redacted] | [redacted] | [redacted] | [redacted] |
| Skeletal Related Events (estimate) | [redacted] | [redacted] | [redacted] | [redacted] |
| Skeletal Morbidity Rate | [redacted] | [redacted] | [redacted] | [redacted] |
| Cycle length (days) | [redacted] | [redacted] | [redacted] | [redacted] |
| Cycle rate | [redacted] | [redacted] | [redacted] | [redacted] |

- Discontinuation rates and SAEs

The base case applies those of the manufacturer model, as summarised in table 77 above. In the absence of any other data, the rates for modelling of lung cancer are assumed to be the same as those for the other solid tumours including lung cancer modelling.

- Quality of life values

Despite the lack of detail around their estimation, the AG views the manufacturer estimates for the quality of life impacts from SREs and SAEs as the best that are available. The balance between the SREs results in average QALY decrement per SRE as outlined below.

**Table 99 SRE distribution and average QALY decrements**

| | Breast cancer | | Prostate cancer | | Other solid tumours | |
|---|---|---|---|---|---|---|
| | SRE naive | SRE exper | SRE naive | SRE exp | SRE naive | SRE exper |
| QALY decrement | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

The lower average SRE QALY decrement between breast cancer patients and the other cancers arises from mainly from the lower proportion of SREs which are either radiation to the bone or spinal cord compression. The average SRE QALY decrement among SRE experienced breast cancer patients is

further affected by non-vertebral fractures being estimated to have a particularly small HRQoL impact for this group. Note the QALY decrements reported above for the SRE naïve patients do not take into account the step change in utility when moving from being SRE naïve to SRE experienced continuing through to death, as outlined in table 83 above.

Modelling a sustained quality of life impact from spinal cord compression beyond the 5 months subsequent to the compression is implemented by calculating the discounted expected cycles of survival from 5 months subsequent to the compression through to the model horizon. This is then multiplied by the per cycle QALY decrement associated with spinal cord compression. The QALY decrement can be either the average or the maximum decrement estimated during the 5 months subsequent to the compression, as outlined in table 83 above.

Modelling a decay in quality of life in the final year adjusts the total within cycle QALY by the proportionate decline in utility as outlined in table 66 above, taking the modelled survival into account. The proportion of patients anticipated to survive to 12 months beyond the cycle requires no adjustment to be made to their QALY. Working back from this, the proportion anticipated to survive to 11 months beyond the cycle has the percentage reduction in utility for being 11 months to death as drawn from table 66, applied. This is worked back through to the proportion anticipated to survive only 1 month beyond the cycle being modelled, which has the proportionate decline in utility for being 1 months to death applied. Summing these gives a total overall QALY multiplier to apply to the total within cycle QALY. For instance, within the first cycle of the breast cancer model this gives rise to a multiplier of 0.96, which by the twelfth cycle has fallen to 0.93.

HRQoL values for SAEs are as per table 85 above. The manufacturer assumption of a permanent decrement from ONJ and renal toxicity has been adopted for the base case, with a sensitivity analysis limiting this to the average duration observed within the trials.

- Resource use

The direct drug and administration costs for the base cases are as per the manufacturer submission, only correcting the zoledronic acid price and the pamidronate price for BNF62. Note that these costings do not attempt to correct for doses of zoledronic acid being withheld due to renal toxicity. Given the uncertainty around the future price of zoledronic acid due to imminent patent expiry a common set of sensitivity analyses are presented that incrementally reduce this price by 5%.

Note that removing the 15 minutes nursing time for zoledronic acid infusion that the manufacturer adds post hoc to the time and motion survey is equivalent to a reduction in the price of zoledronic acid

of around 7%. In the light of this, sensitivity analyses around zoledronic acid administration costs have not been separately presented.

In common with the Ross HTA[55] and the manufacturer submission, the AG costings of events rely to a large extent upon averaging reference costs, coupled with some expert opinion on the balance between the proportion of patients admitted as a result of the event and the proportion treated as either day cases or outpatients. As already noted, the manufacturer costings include excess bed days on the basis of the trim point being the average length of stay. These have been excluded from the AG costings, with the exception of the SCC costing.

For SCC NICE CG75 suggests an average £892 [£844] for patient rehabilitation drawn from CG75. Even this may still underestimate the full cost of SCC, given that a proportion of patients will be to a greater or lesser extent paralysed require ongoing care.

Costs for SAEs are less in line with those of the manufacturer, mainly due to the manufacturer typically assuming that all would be treated on an inpatient basis, though this does include a proportion of day cases. AG expert opinion suggests that an elective or non-elective inpatient admission is unlikely for ONJ, skin infections or renal toxicity caused by bisphosphonate use. In the light of this ONJ has been costed on the basis of being treated as 90% day case with the remainder being admitted; skin infections on the basis of 90% being treated as outpatients with one initial and two follow-up appointments; and, renal toxicity on the basis of 90% being treated as outpatients with one initial and two follow-up appointments with the remainder being treated as day cases. Sensitivity analyses find these distinctions to have relatively little impact.

**Table 100 SRE and SAE event costs**

| **SREs** | AG | Manufacturer |
|---|---|---|
| Vertebral fracture | £294 | [redacted] |
| Non-vertebral fracture | £1,581 | [redacted] |
| Radiation to the bone | £662 | [redacted] |
| Surgery to the bone | £7,269 | [redacted] |
| Spinal cord compression | £7,311 | [redacted] |
| **SAEs** | | |
| ONJ | £1,220 | £2,465 |
| Renal | £496 | £1,681 |
| Hypercalcaemia | £4,579 | £4,579 |
| Hypocalcaemia | £443 | £443 |
| Skin | £370 | £1,440 |
| *£5,261 based on average NHS reference costs | | |

As in the manufacturer base case, the cost of vertebral fractures is set to zero on the basis that most are sufficiently asymptomatic to not require treatment. Within the probabilistic modelling the rates of SREs are treated probabilistically, but the unit costs are treated deterministically.

*Univariate sensitivity analyses*

A range of univariate sensitivity analyses are presented for the lifetime cost utility modelling.

**Table 101 Univariate sensitivity analyses conducted**

| **Description** | **Abbreviated** |
|---|---|
| Base Case | Base Case |
| Amgen STARs costing | Amgen STARs |
| Amgen NMA results | Amgen NMA |
| Amgen STARs costings and NMA results | Amgen STARs+NMA |
| No HRQoL step change for naive to experienced | No Naive util step |
| SCC permanent utility effect of the average P1-P5 decrement | SCC ongoing mean |
| SCC permanent utility effect of the maximum P1-P5 decrement | SCC ongoing max |
| No general mortality | No gen. mortality |
| 5 year horizon | 5 year horizon |
| 2 year horizon | 2 year horizon |
| van den Hout utility multipliers for last year of life | vd Hout utility |
| Excluding ONJ and renal toxicity utility impact beyond trial average | No SAE P1+ |
| Excluding SAEs | No SAE |

| Description | Abbreviated |
|---|---|
| No general discontinuations | No gen. discs. |
| No discontinuations | No discs. |
| AG TTF functional form from NAIVE for breast and prostate | TTF form AG naive |
| AG TTF functional form all patients for breast, prostate and OSTL | TTF form AG all patients |

The results of these are presented in full for all patients, for SRE naïve patients and for SRE experienced patients for the comparison of denosumab with zoledronic acid and for the comparison of denosumab with BSC. But given the results of the analyses for the comparisons with BSC result in cost effectiveness estimates typically in excess of £100k per QALY even with the PAS, these are generally not reported in the main body of the text. For the sake of space, the body of the report only presents the summary of these for all patients for breast cancer, and all patients and SRE experienced patients for the remaining analyses. Where the sensitivity analysis results in a cost effectiveness estimate for denosumab versus BSC of less than £50k per QALY this is individually reported in the text, and whether this applies to all patients, SRE naïve patients or SRE experienced patients.

In addition to these, given the zoledronic acid is shortly coming off patent the impact of a range of reductions in the price of zoledronic acid are also reported.

- Presentation of results

For the lifetime cost utility modelling a common format has been adopted for each of the four cancers groups being modelled. The results of the base case deterministic modelling that apply the AG NMA results are presented in detail, coupled with the associated cost-effectiveness acceptability frontiers (CEAFs) from the probabilistic modelling. The range of univariate sensitive analyses are then tabulated, followed by a summary of the main point arising from them and of the impact of reductions in the price of zoledronic acid. This is then followed by a detailed presentation of results from the application of the SRE naïve and SRE experienced specific hazard ratios and relative risks. This latter is as per the base case, only with the SRE naïve and SRE experienced specific hazard ratios and relative risks for denosumab versus zoledronic acid being applied, as summarised in table 76 above.

### *11.3.2 Results*

*Within trial data analysis*

Using data from the CSRs and the submission permits the average number of doses administered and the numbers of SREs to be presented, together with the numbers of SAEs, for each arm. The following presents these on the basis of net number of events per patient year together with their costs, coupled with the average number of drug administrations per patient year and the costs of this.

In order to cost the SREs and SAEs, and to assess their QALY impact, the individual events can be assessed separately. But this may result in the analysis being driven by a very small net difference in costly events between the arms. In line with the economic modelling, the same average distribution between SREs can be assumed for each arm. The resulting average SRE unit cost and average SRE QALY impact can then be applied to the net difference between the arms. This latter will be referred to as average event based, the former individual event based. The average total QALY decrements per event are drawn from the manufacturer submission as summarised above.

- Breast cancer

The direct on trial drug and administration costs are as below.

**Table 102 Breast cancer trial based annual results**

| | **Zol Acid** | **Denos** | | | | | |
|---|---|---|---|---|---|---|---|
| Patient years | [redacted] | [redacted] | | Unit | | QALY | |
| N (full analysis set) | [redacted] | [redacted] | Net p.a. | Cost | Net p.a. | decr. | Net p.a. |
| SREs average event | [redacted] | [redacted] | [redacted] | £1,222 | [redacted] | [redacted] | 0.003 |
| SCC | [redacted] | [redacted] | [redacted] | £7,311 | | [redacted] | |
| Surgery to bone | [redacted] | [redacted] | [redacted] | £7,269 | | [redacted] | |
| Fracture | [redacted] | [redacted] | [redacted] | £895 | | [redacted] | |
| Radiation to bone | [redacted] | [redacted] | [redacted] | £662 | | [redacted] | |
| SREs individual event | | | | | [redacted] | | 0.005 |
| N (safety set) | [redacted] | [redacted] | | | | | |
| SAEs average event | [redacted] | [redacted] | [redacted] | £1,396 | [redacted] | [redacted] | 0.000 |
| ONJ | [redacted] | [redacted] | [redacted] | £1,220 | | [redacted] | |
| Renal toxicity | [redacted] | [redacted] | [redacted] | £496 | | [redacted] | |
| Hypercalcaemia | [redacted] | [redacted] | [redacted] | £4,579 | | [redacted] | |
| Hypocalcaemia | [redacted] | [redacted] | [redacted] | £443 | | [redacted] | |
| Skin infection | [redacted] | [redacted] | [redacted] | £370 | | [redacted] | |
| SAEs individual event | | | | | [redacted] | | 0.001 |
| Mean administrations | [redacted] | [redacted] | | | | | |
| Per patient year | [redacted] | [redacted] | | | | | |
| drug & admin ex PAS | [redacted] | [redacted] | | | [redacted] | | |
| drug & admin inc PAS | [redacted] | [redacted] | | | [redacted] | | |

This can be further summarised:

**Table 103 Breast cancer trial based annual cost effectiveness**

| | Average event assessment | | | Individual event assessment | | |
|---|---|---|---|---|---|---|
| | **Costs** | **QALYs** | **ICER** | **Costs** | **QALYs** | **ICER** |
| Results excluding PAS | £1,098 | 0.003 | £378,487 | £1,147 | 0.006 | £190,841 |
| Results including PAS | -£26 | 0.003 | Dominant | £23 | 0.006 | £3,783 |

This analysis is relatively straightforward and sees denosumab increase total costs by between £1,101 and £1,149 compared to zoledronic acid. This suggests crude estimates of the on trial cost effectiveness excluding the PAS of between £191k and £378k per QALY compared to zoledronic acid. But with the PAS denosumab is estimated to be broadly cost neutral, with this ranging between a cost saving of £26 to a small additional cost of £23 depending upon how the costs of SREs and SAEs are summed. This results in denosumab being estimated to range from dominating zoledronic acid to having a very acceptable cost effectiveness ratio of £3,783 per QALY.

Due to the small QALY gains estimated in the above, relatively small changes in the price of zoledronic acid cause quite large changes in the cost effectiveness estimates. [redacted]

- Prostate cancer

The direct on trial drug and administration costs are as below.

**Table 104 Prostate cancer trial based annual results**

| | Zol Acid | Denos | | | | | |
|---|---|---|---|---|---|---|---|
| Patient years | [redacted] | [redacted] | Net p.a. | Unit Cost | Net p.a. | QALY decr. | Net p.a. |
| N (full analysis set) | [redacted] | [redacted] | | | | | |
| SREs average event | [redacted] | [redacted] | [redacted] | £1,247 | [redacted] | [redacted] | 0.008 |
| SCC | [redacted] | [redacted] | [redacted] | £7,311 | | [redacted] | |
| Surgery to bone | [redacted] | [redacted] | [redacted] | £7,269 | | [redacted] | |
| Fracture | [redacted] | [redacted] | [redacted] | £694 | | [redacted] | |
| Radiation to bone | [redacted] | [redacted] | [redacted] | £662 | | [redacted] | |
| SREs individual event | | | | | [redacted] | | 0.016 |
| N( safety set) | [redacted] | [redacted] | | | | | |
| SAEs average event | [redacted] | [redacted] | [redacted] | £857 | [redacted] | [redacted] | -0.001 |
| ONJ | [redacted] | [redacted] | [redacted] | £1,220 | | [redacted] | |
| Renal toxicity | [redacted] | [redacted] | [redacted] | £496 | | [redacted] | |
| Hypercalcaemia | [redacted] | [redacted] | [redacted] | £4,579 | | [redacted] | |
| Hypocalcaemia | [redacted] | [redacted] | [redacted] | £443 | | [redacted] | |
| Skin infection | [redacted] | [redacted] | [redacted] | £370 | | [redacted] | |
| SAEs individual event | | | | | [redacted] | | 0.000 |
| Mean administrations | [redacted] | [redacted] | | | | | |
| Per patient year | [redacted] | [redacted] | | | | | |
| drug & admin ex PAS | [redacted] | [redacted] | | | [redacted] | | |
| drug & admin inc PAS | [redacted] | [redacted] | | | [redacted] | | |

This can be further summarised:

**Table 105 Prostate cancer trial based annual cost effectiveness**

| | Average event assessment | | | Individual event assessment | | |
|---|---|---|---|---|---|---|
| | **Costs** | **QALYs** | **ICER** | **Costs** | **QALYs** | **ICER** |
| Results excluding PAS | £1,214 | 0.007 | £165,881 | £1,228 | 0.016 | £77,129 |
| Results including PAS | £111 | 0.007 | £15,190 | £126 | 0.016 | £7,904 |

Again, the principal immediate uncertainty may relate to the cost of zoledronic acid.

As for breast cancer, this analysis for prostate cancer is relatively straightforward and sees denosumab increase total costs by between £1,214 and £1,228 compared to zoledronic acid. This suggests crude estimates of the on trial cost effectiveness excluding the PAS of between £77k and £166k per QALY compared to zoledronic acid. Within this analysis there is a greater absolute QALY discrepancy between the average event based analysis and the individual event based analysis. This arises in large part due to the crude estimate of the impact upon the annual incidence of spinal cord compression. Whether this is an argument for assessing the SREs on an individual event basis is a moot point, but it seems conceivable that there may be different effects in osteolytic cancers compared to osteoblastic cancers.

With the PAS denosumab is estimated to result in an average cost increase of between £111 and £126 per annum. Given the differences in the QALY estimates, this results in cost effectiveness estimates ranging between £7,904 per QALY and £15,190 per QALY. Due to the small QALY gains estimated using the average event based method, as for breast cancer relatively small changes in the price of zoledronic acid cause large changes in the cost effectiveness. With the PAS, a fall in the price of zoledronic acid of between [redacted] in the average event analysis and [redacted] in the individual event analysis would be sufficient to make the additional cost of denosumab not justify the relatively small average QALY gains.

- Other solid tumours excluding multiple myeloma

Unfortunately, the CSR, the manufacturer model and the submission do not provide sufficient detail to be able to present this analysis for the patient group of other solid tumours excluding multiple myeloma.

*Cost utility modelling*

- Breast cancer base case

The modelling that applies the AG NMA results in the following:

**Table 106 Breast cancer AG NMA cost effectiveness results**

| **All Patients** | SREs | net | QALYs | net | Tx Costs | net | All Costs | net | ICER |
|---|---|---|---|---|---|---|---|---|---|
| BSC | 3.318 | -1.085 | 1.819 | 0.027 | [redacted] | [redacted] | [redacted] | £6,114 | £224,411 |
| inc PAS | | | | | | [redacted] | | £4,165 | £152,847 |
| Zol. Acid | 2.466 | -0.233 | 1.833 | 0.013 | [redacted] | [redacted] | [redacted] | £1,680 | £126,821 |
| inc PAS | | | | | | [redacted] | | -£270 | Dominant |
| Denosumab | 2.233 | | 1.846 | | [redacted] | | [redacted] | | |
| inc PAS | | | | | [redacted] | | [redacted] | | |
| Pamidronate | 2.553 | -0.320 | 1.832 | 0.014 | [redacted] | [redacted] | [redacted] | -£1,367 | Dominant |
| inc PAS | | | | | | [redacted] | | -£3,317 | Dominant |
| **SRE Naive** | SREs | net | QALYs | net | Tx Costs | net | All Costs | net | ICER |
| BSC | 2.918 | -1.028 | 1.848 | 0.034 | [redacted] | [redacted] | [redacted] | £6,223 | £181,007 |
| inc PAS | | | | | | [redacted] | | £4,273 | £124,291 |
| Zol. Acid | 2.095 | -0.204 | 1.868 | 0.015 | [redacted] | [redacted] | [redacted] | £1,725 | £117,186 |
| inc PAS | | | | | | [redacted] | | -£225 | Dominant |
| Denosumab | 1.890 | | 1.883 | | [redacted] | | [redacted] | | |
| inc PAS | | | | | [redacted] | | [redacted] | | |
| Pamidronate | 2.055 | -0.164 | 1.870 | 0.013 | [redacted] | [redacted] | [redacted] | -£1,156 | Dominant |
| inc PAS | | | | | | [redacted] | | -£3,106 | Dominant |
| **SRE Exper** | SREs | net | QALYs | net | Tx Costs | net | All Costs | net | ICER |
| BSC | 3.894 | -1.167 | 1.776 | 0.017 | [redacted] | [redacted] | [redacted] | £5,958 | £350,856 |
| inc PAS | | | | | | [redacted] | | £4,008 | £236,037 |
| Zol. Acid | 3.000 | -0.273 | 1.782 | 0.011 | [redacted] | [redacted] | [redacted] | £1,615 | £145,171 |
| inc PAS | | | | | | [redacted] | | -£335 | Dominant |
| Denosumab | 2.727 | | 1.793 | | [redacted] | | [redacted] | | |
| inc PAS | | | | | [redacted] | | [redacted] | | |
| Pamidronate | 3.270 | -0.543 | 1.776 | 0.017 | [redacted] | [redacted] | [redacted] | -£1,670 | Dominant |
| inc PAS | | | | | | [redacted] | | -£3,620 | Dominant |

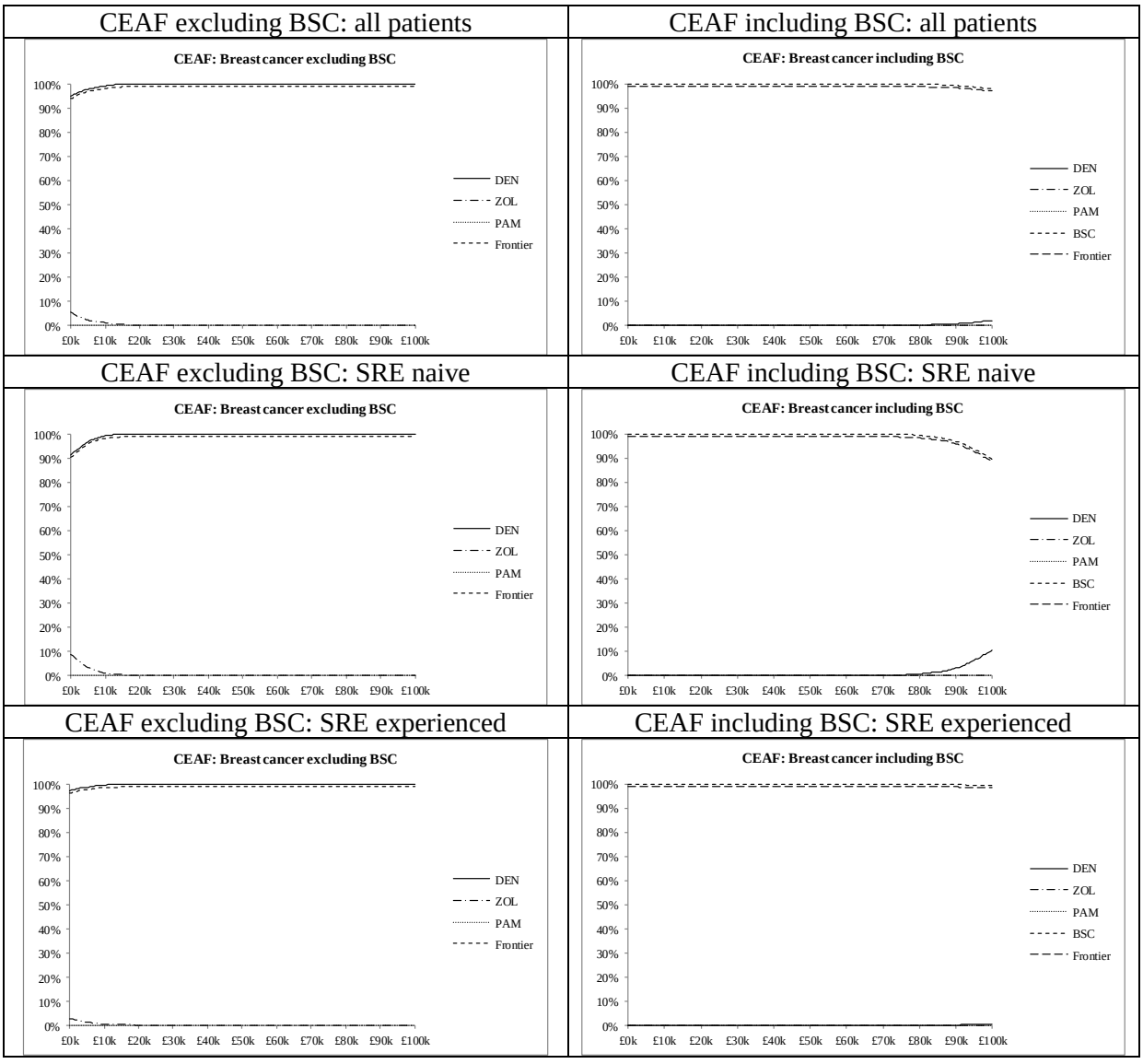
The net gain from denosumab over zoledronic acid of 0.013 QALYs is actually somewhat higher than that estimated by the manufacturer. This may be due to the treatment of utilities during the first five months of the modelling. But this remains a relatively small gain, which without the PAS requires an additional £1,680 resulting in a cost effectiveness of £126,821 per QALY.

For those contraindicated to bisphosphonates the cost effectiveness of denosumab compared to BSC is worse. Patient gains are larger at 0.027 QALYs but the net cost rises by a greater amount to £6,114 resulting in a cost effectiveness estimate of £224,411 per QALY.

With the PAS, the anticipated cost savings are less than anticipated by the manufacturer but this appears to be broadly in line with the assumed costs of SREs and SAEs. Given the cost saving and the anticipated patient gains, denosumab is estimated to dominate zoledronic acid. Probabilistic modelling over 2,000 iterations is broadly in line with this, estimating the same 0.013 QALYs, but a slightly smaller average cost saving of £267.

For those contraindicated to bisphosphonates, the cost effectiveness of denosumab compared to BSC is again considerably worse, with a central estimate across all these patients of £152,847 per QALY. Across all patients the probabilistic modelling suggests similar central estimates of 0.027 QALYs and a net cost of £4,163 to yield a cost effectiveness estimate of £151,778 per QALY.

**Figure 13 Breast cancer CEAFs including the PAS**



- Breast cancer sensitivity analyses

The univariate sensitivity analyses for the all patient modelling for the cost effectiveness of denosumab compared to zoledronic acid are presented below

**Table 107 Breast cancer univariate sensitivity analyses: All patients**

| | Ex PAS | Inc PAS | SREs | QALYs | ICER ex | ICER inc |
|---|---|---|---|---|---|---|
| Base Case | £1,680 | -£270 | -0.233 | 0.013 | £126,821 | Dominant |
| Amgen STARs | £1,635 | -£315 | -0.233 | 0.013 | £123,422 | Dominant |
| Amgen NMA | £1,705 | -£245 | -0.213 | 0.013 | £133,556 | Dominant |
| Amgen STARs+NMA | £1,664 | -£286 | -0.213 | 0.013 | £130,322 | Dominant |
| No Naive util step | £1,680 | -£270 | -0.233 | 0.011 | £155,331 | Dominant |
| SCC ongoing mean | £1,680 | -£270 | -0.233 | 0.015 | £115,025 | Dominant |
| SCC ongoing max | £1,680 | -£270 | -0.233 | 0.015 | £111,687 | Dominant |
| No gen. mortality | £1,680 | -£270 | -0.233 | 0.013 | £126,821 | Dominant |
| 5 year horizon | £1,644 | -£254 | -0.219 | 0.011 | £145,347 | Dominant |
| 2 year horizon | £1,291 | -£170 | -0.152 | 0.006 | £216,260 | Dominant |
| vd Hout utility | £1,680 | -£270 | -0.233 | 0.012 | £137,104 | Dominant |
| No SAE P1+ | £1,680 | -£270 | -0.233 | 0.008 | £223,916 | Dominant |
| No SAE | £1,745 | -£230 | -0.236 | 0.007 | £263,627 | Dominant |
| No gen. discs. | £3,120 | -£461 | -0.438 | 0.023 | £136,300 | Dominant |
| No discs. | £3,189 | -£470 | -0.448 | 0.023 | £136,702 | Dominant |
| TTF form AG naive | £1,680 | -£270 | -0.232 | 0.013 | £126,523 | Dominant |
| TTF form AG all | £1,658 | -£292 | -0.250 | 0.014 | £118,941 | Dominant |

The sensitivity analyses suggest that the assessment group estimates and manufacturer estimates are broadly in line. Applying the manufacturer estimates for costs and effectiveness have little impact, while applying the assessment group estimates for the functional form for the time to first SRE again has very little impact.

The main sensitivity of results is around the SAEs and the discontinuation rates. Given the higher rate of renal failure within the zoledronic acid arm removing the assumed ongoing utility decrement associated with this and ONJ reduces the anticipated benefits from denosumab by around a third to up to one half, with a parallel adverse impact upon the cost effectiveness estimate. Excluding discontinuations also has quite a large impact, though the increase in the net patient gains is broadly mirrored by an increase in the net cost resulting in a relatively static ICER.

A reduction in the price of zoledronic acid of 10% results in the cost effectiveness of denosumab compared to zoledronic acid across all breast cancer patients including the PAS [redacted].

Applying the head to head SRE naïve and SRE specific clinical effectiveness results for denosumab versus zoledronic acid, while retaining the remainder of the AG NMA results in the following.

**Table 108 Breast cancer SRE patient subgroup effects cost effectiveness results**

| **All Patients** | SREs | net | QALYs | net | Tx Costs | net | All Costs | net | ICER |
|---|---|---|---|---|---|---|---|---|---|
| BSC | 3.318 | -1.074 | 1.819 | 0.026 | [redacted] | [redacted] | [redacted] | £6,126 | £233,015 |
| inc PAS | | | | | | [redacted] | | £4,176 | £158,844 |
| Zol. Acid | 2.466 | -0.222 | 1.833 | 0.012 | [redacted] | [redacted] | [redacted] | £1,691 | £137,625 |
| inc PAS | | | | | | [redacted] | | -£259 | Dominant |
| Denosumab | 2.244 | | 1.845 | | [redacted] | | [redacted] | | |
| inc PAS | | | | | [redacted] | | [redacted] | | |
| Pamidronate | 2.553 | -0.309 | 1.832 | 0.013 | [redacted] | [redacted] | [redacted] | -£1,355 | Dominant |
| inc PAS | | | | | | [redacted] | | -£3,305 | Dominant |
| **SRE Naive** | SREs | net | QALYs | net | Tx Costs | net | All Costs | net | ICER |
| BSC | 2.918 | -0.998 | 1.848 | 0.033 | [redacted] | [redacted] | [redacted] | £6,258 | £192,177 |
| inc PAS | | | | | | [redacted] | | £4,308 | £132,297 |
| Zol. Acid | 2.095 | -0.175 | 1.868 | 0.013 | [redacted] | [redacted] | [redacted] | £1,760 | £136,390 |
| inc PAS | | | | | | [redacted] | | -£190 | Dominant |
| Denosumab | 1.920 | | 1.881 | | [redacted] | | [redacted] | | |
| inc PAS | | | | | [redacted] | | [redacted] | | |
| Pamidronate | 2.055 | -0.135 | 1.870 | 0.011 | [redacted] | [redacted] | [redacted] | -£1,121 | Dominant |
| inc PAS | | | | | | [redacted] | | -£3,071 | Dominant |
| **SRE Exper** | SREs | net | QALYs | net | Tx Costs | net | All Costs | net | ICER |
| BSC | 3.894 | -1.184 | 1.776 | 0.017 | [redacted] | [redacted] | [redacted] | £5,936 | £343,887 |
| inc PAS | | | | | | [redacted] | | £3,986 | £230,917 |
| Zol. Acid | 3.000 | -0.290 | 1.782 | 0.011 | [redacted] | [redacted] | [redacted] | £1,592 | £139,635 |
| inc PAS | | | | | | [redacted] | | -£358 | Dominant |
| Denosumab | 2.710 | | 1.793 | | [redacted] | | [redacted] | | |
| inc PAS | | | | | [redacted] | | [redacted] | | |
| Pamidronate | 3.270 | -0.560 | 1.776 | 0.017 | [redacted] | [redacted] | [redacted] | -£1,693 | Dominant |
| inc PAS | | | | | | [redacted] | | -£3,642 | Dominant |

For breast cancer, as the subgroup specific hazard ratios and relative risks for denosumab compared to zoledronic acid are broadly similar to the estimates pooled across all patients, applying the subgroup specific hazard ratios and relative risks has relatively limited impact upon results.

- Prostate cancer base case

The modelling that applies the AG NMA results in the following:

**Table 109 Prostate cancer AG NMA cost effectiveness results**

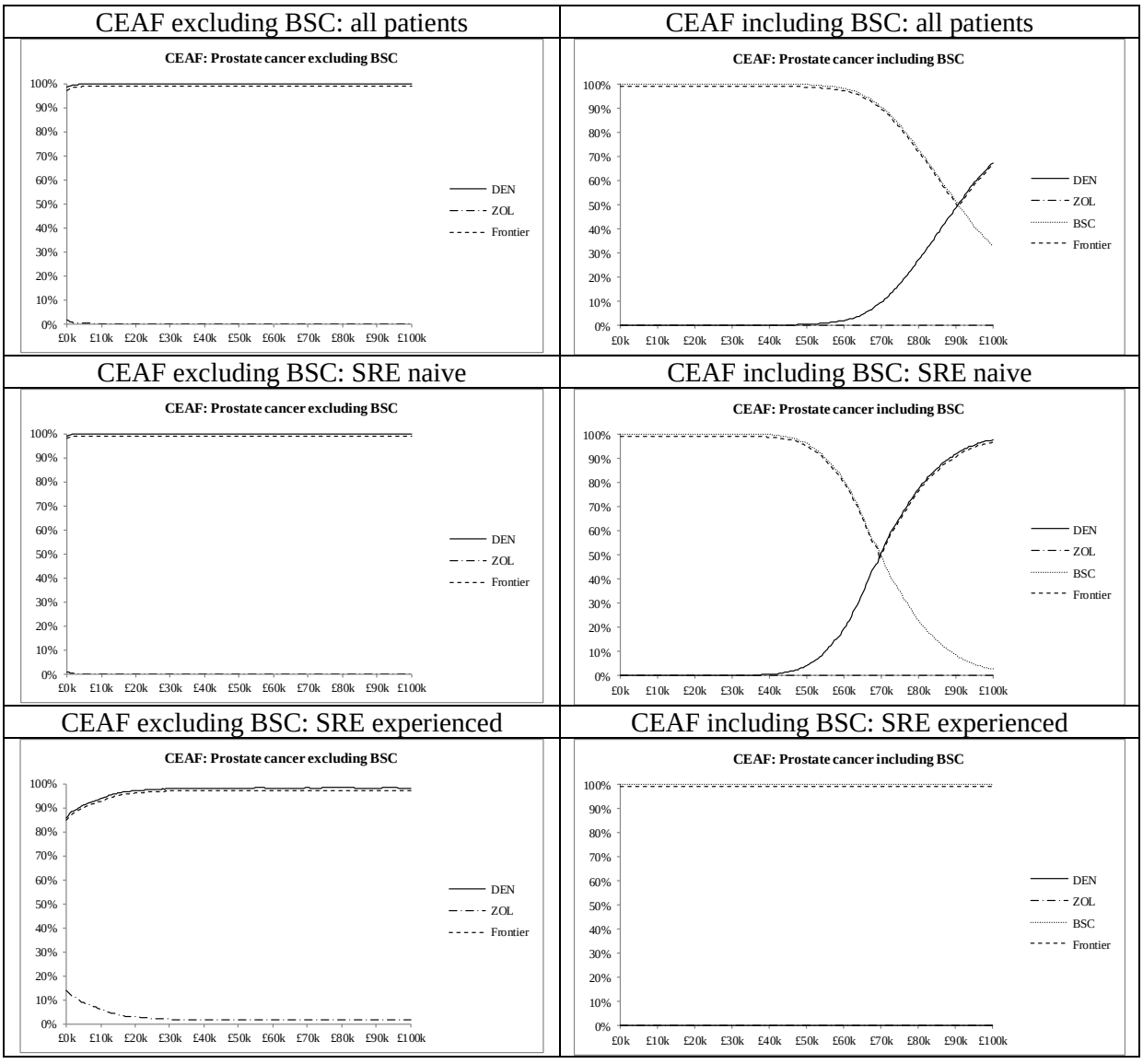
| **All Patients** | SREs | net | QALYs | net | Tx Costs | net | All Costs | net | ICER |
|---|---|---|---|---|---|---|---|---|---|
| BSC | 2.089 | -0.601 | 1.068 | 0.030 | [redacted] | [redacted] | [redacted] | £3,880 | £130,674 |
| inc PAS | | | | | | [redacted] | | £2,695 | £90,788 |
| Zol. Acid | 1.716 | -0.228 | 1.077 | 0.020 | [redacted] | [redacted] | [redacted] | £941 | £46,976 |
| inc PAS | | | | | | [redacted] | | -£243 | Dominant |
| Denosumab | 1.488 | .. | 1.097 | | [redacted] | | [redacted] | | |
| inc PAS | | | | | [redacted] | | [redacted] | | |
| **SRE Naive** | SREs | net | QALYs | net | Tx Costs | net | All Costs | net | ICER |
| BSC | 1.976 | -0.641 | 1.091 | 0.038 | [redacted] | [redacted] | [redacted] | £3,832 | £100,601 |
| inc PAS | | | | | | [redacted] | | £2,648 | £69,510 |
| Zol. Acid | 1.600 | -0.265 | 1.104 | 0.025 | [redacted] | [redacted] | [redacted] | £897 | £35,732 |
| inc PAS | | | | | | [redacted] | | -£287 | Dominant |
| Denosumab | 1.335 | .. | 1.129 | | [redacted] | | [redacted] | | |
| inc PAS | | | | | [redacted] | | [redacted] | | |
| **SRE Exper** | SREs | net | QALYs | net | Tx Costs | net | All Costs | net | ICER |
| BSC | 2.395 | -0.493 | 1.006 | 0.007 | [redacted] | [redacted] | [redacted] | £4,009 | £574,364 |
| inc PAS | | | | | | [redacted] | | £2,825 | £404,707 |
| Zol. Acid | 2.030 | -0.128 | 1.006 | 0.006 | [redacted] | [redacted] | [redacted] | £1,061 | £167,503 |
| inc PAS | | | | | | [redacted] | | -£123 | Dominant |
| Denosumab | 1.902 | .. | 1.012 | | [redacted] | | [redacted] | | |
| inc PAS | | | | | [redacted] | | [redacted] | | |

Larger patient gains are anticipated for prostate cancer patients. This arises in part due to the higher proportion of spinal cord compressions within the overall incidence of SREs. But the analysis is broadly similar to that for breast cancer. Without the PAS, the relatively small patient gain of 0.020 QALYs at an additional cost of £941 results in a cost effectiveness compared to zoledronic acid of £46,976 per QALY. But with the PAS, cost savings and dominance over zoledronic acid are anticipated.

The cost effectiveness is estimated to be slightly worse among the SRE experienced than across the patient group as a whole, though this may be due in part to the step change in HRQoL that is applied when SRE naïve patients experience their first SRE. But with the PAS, cost savings are again anticipated which again results in dominance over zoledronic acid. The probabilistic modelling suggests central estimates of a gain of 0.020 QALYs and a cost saving of £244 across all patients.

For those contraindicated to bisphosphonates, even with the PAS the cost effectiveness of denosumab compared to BSC is poor at between £70k per QALY and £405k per QALY. Across all patients the probabilistic modelling suggests similar central estimates of 0.030 QALYs and a net cost of £2,694 to yield a cost effectiveness estimate of £90,067 per QALY.

**Figure 14 Prostate cancer CEAFs including the PAS**



- Prostate cancer sensitivity analyses

The univariate sensitivity analyses for the SRE experienced patient modelling for the cost effectiveness of denosumab are presented overleaf.

**Table 110 Prostate cancer univariate sensitivity analyses: All patients and SRE experienced patients**

| | SRE naïve patients vs BSC | | | | | | SRE experienced patients vs zoledronic acid | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Ex PAS | Inc PAS | SREs | QALYs | ICER ex | ICER inc | Ex PAS | Inc PAS | SREs | QALYs | ICER ex | ICER inc |
| Base Case | £3,832 | £2,648 | -0.641 | 0.038 | £100,601 | £69,510 | £1,061 | -£123 | -0.128 | 0.006 | £167,503 | Dominant |
| Amgen STARs | £3,737 | £2,553 | -0.641 | 0.038 | £98,116 | £67,026 | £1,034 | -£150 | -0.128 | 0.006 | £163,303 | Dominant |
| Amgen NMA | £3,965 | £2,780 | -0.532 | 0.025 | £159,682 | £111,985 | £1,054 | -£130 | -0.134 | 0.007 | £159,601 | Dominant |
| Amgen STARs+NMA | £3,903 | £2,719 | -0.532 | 0.025 | £157,215 | £109,518 | £1,026 | -£159 | -0.134 | 0.007 | £155,319 | Dominant |
| No naive util step | £3,832 | £2,648 | -0.641 | 0.019 | £206,119 | £142,418 | £1,061 | -£123 | -0.128 | 0.006 | £167,503 | Dominant |
| SCC ongoing mean | £3,832 | £2,648 | -0.641 | 0.051 | £74,759 | £51,655 | £1,061 | -£123 | -0.128 | 0.009 | £117,299 | Dominant |
| SCC ongoing max | £3,832 | £2,648 | -0.641 | 0.060 | £63,543 | £43,905 | £1,061 | -£123 | -0.128 | 0.011 | £97,267 | Dominant |
| No gen. mortality | £3,832 | £2,648 | -0.641 | 0.038 | £100,601 | £69,510 | £1,061 | -£123 | -0.128 | 0.006 | £167,503 | Dominant |
| 5 year horizon | £3,826 | £2,646 | -0.631 | 0.039 | £98,575 | £68,171 | £1,058 | -£122 | -0.128 | 0.006 | £169,582 | Dominant |
| 2 year horizon | £3,499 | £2,433 | -0.526 | 0.035 | £101,245 | £70,399 | £966 | -£100 | -0.116 | 0.005 | £176,496 | Dominant |
| vd Hout utility | £3,832 | £2,648 | -0.641 | 0.033 | £115,708 | £79,948 | £1,061 | -£123 | -0.128 | 0.006 | £191,385 | Dominant |
| No SAE P1+ | £3,832 | £2,648 | -0.641 | 0.052 | £73,450 | £50,750 | £1,061 | -£123 | -0.128 | 0.006 | £181,229 | Dominant |
| No SAE | £3,844 | £2,634 | -0.654 | 0.055 | £69,360 | £47,533 | £1,084 | -£126 | -0.135 | 0.006 | £169,539 | Dominant |
| No gen. discs. | £7,397 | £5,139 | -1.179 | 0.062 | £119,273 | £82,856 | £2,002 | -£257 | -0.255 | 0.013 | £159,370 | Dominant |
| No discs. | £7,700 | £5,351 | -1.223 | 0.064 | £120,768 | £83,926 | £2,189 | -£161 | -0.281 | 0.013 | £166,078 | Dominant |
| TTF form AG naive | £3,868 | £2,684 | -0.608 | 0.036 | £108,353 | £75,184 | £1,061 | -£123 | -0.128 | 0.006 | £167,503 | Dominant |
| TTF form AG all | £3,813 | £2,629 | -0.657 | 0.039 | £96,748 | £66,701 | £1,061 | -£123 | -0.128 | 0.006 | £167,503 | Dominant |

One of the main sensitivities relates to the application of the manufacturer NMA results which halves the patient benefits associated with denosumab. This is as would be expected given the HR for the time to first SRE of 0.82 compared to the assessment group network meta-analysis estimate of 0.57. Note that this only affects the SRE naïve patients. The relative risks for subsequent SREs are more in line at [redacted] for the manufacturer and 0.83 for the assessment group NMA and as a consequence there is little impact among SRE experienced patients.

Prostate cancer patient benefits are more sensitive to the assumed duration of the quality of life impact from spinal cord compression than breast cancer patients. The anticipated net QALY gain from denosumab compared to zoledronic acid increases by up to around 40% depending upon whether the mean decrement post diagnosis or the maximum decrement post diagnosis is carried forward.

If the average (or maximum) spinal cord compression utility decrement is carried forward in the modelling for SRE naïve prostate patients this yield a cost effectiveness estimate for denosumab with the PAS compared to BSC of £51,655 per QALY (or £43,905 per QALY). There is limited data on the rates of paralysis from spinal cord compression and the cost estimates from averaging reference costs may be too low. CG75 suggests an average therapy cost of £14,173 [£13,705]. Adding this to the average rehabilitation costs and applying the average spinal cord compression decrement through to death results in a cost effectiveness estimate for the with PAS analysis for SRE naïve prostate patients of [redacted] per QALY compared to BSC, and [redacted] per QALY when applying the maximum decrement. But within the analyses that apply the SRE subgroup specific hazards these estimates rise to [redacted] per QALY and [redacted] respectively.

A concern within the modelling is BSC being assumed to have a zero incidence of the modelled SAEs. When the benefits from active treatments upon SREs are muted, there is the possibility that SAEs come to the fore and require a more detailed consideration. Sensitivity analyses that completely exclude SAEs from the analysis do improve the cost effectiveness of denosumab compared to BSC, but this in itself is not sufficient to render denosumab cost effective. Even with the PAS, all but one of the cost effectiveness estimates remain above £50k per QALY with a large majority being above £100k per QALY. The exception is the cost effectiveness estimate for SRE naïve prostate cancer patients, which within the pooled clinical effectiveness estimates analysis sees denosumab have a cost effectiveness estimate compared to BSC of £47,533 per QALY when all SAEs are excluded from the analysis.

As for the breast cancer modelling removing treatment discontinuations increases the net gain from denosumab over zoledronic acid, though this may be better viewed in effect as fewer patients receiving BSC. The net impact on the ICER is quite muted as net costs change roughly in proportion,

but note that it tends to worsen the cost effectiveness for the comparison with BSC but improve it for the comparison with zoledronic acid.

A reduction in the price of zoledronic acid of 10% results in the cost effectiveness of denosumab compared to zoledronic acid for SRE experienced prostate cancer patients including the PAS [redacted].

Applying the head to head SRE naïve and SRE specific clinical effectiveness results for denosumab versus zoledronic acid, while retaining the remainder of the AG NMA results in the following.

**Table 111 Prostate cancer SRE patient subgroup effects cost effectiveness results**

| **All Patients** | SREs | net | QALYs | net | Tx Costs | net | All Costs | net | ICER |
|---|---|---|---|---|---|---|---|---|---|
| BSC | 2.089 | -0.487 | 1.068 | 0.019 | [redacted] | | | £4,016 | £209,541 |
| inc PAS | | | | | | | | £2,832 | £147,750 |
| Zol. Acid | 1.716 | -0.114 | 1.077 | 0.010 | | | | £1,078 | £113,237 |
| inc PAS | | | | | | | | -£107 | Dominant |
| Denosumab | 1.602 | | 1.087 | | | | | | |
| inc PAS | | | | | | | | | |
| **SRE Naive** | SREs | net | QALYs | net | Tx Costs | net | All Costs | net | ICER |
| BSC | 1.976 | -0.500 | 1.091 | 0.024 | [redacted] | | | £4,001 | £164,155 |
| inc PAS | | | | | | | | £2,816 | £115,564 |
| Zol. Acid | 1.600 | -0.124 | 1.104 | 0.011 | | | | £1,066 | £93,575 |
| inc PAS | | | | | | | | -£118 | Dominant |
| Denosumab | 1.476 | | 1.115 | | | | | | |
| inc PAS | | | | | | | | | |
| **SRE Exper** | SREs | net | QALYs | net | Tx Costs | net | All Costs | net | ICER |
| BSC | 2.395 | -0.453 | 1.006 | 0.005 | [redacted] | | | £4,057 | £797,197 |
| inc PAS | | | | | | | | £2,873 | £564,495 |
| Zol. Acid | 2.030 | -0.088 | 1.006 | 0.004 | | | | £1,109 | £249,575 |
| inc PAS | | | | | | | | -£76 | Dominant |
| Denosumab | 1.942 | | 1.011 | | | | | | |
| inc PAS | | | | | | | | | |

Cost effectiveness results for prostate cancer are more sensitive to the application of the SRE naive and SRE experienced specific hazard ratios and relative risks. Note that within the modelling the impact of this upon the average cost effectiveness across all patients does not broadly cancel out. This is because over the period of extrapolation SRE naïve patients experience SREs and so cross over to

the SRE experienced group. The baseline balance between SRE naïve and SRE experienced patients as drawn from the trial trends towards SRE experienced patients as extrapolation within the model progresses. This also explains why applying the SRE specific estimates worsens the cost effectiveness estimate among those who were SRE naïve at baseline.

But with the PAS denosumab is still estimated to be cost saving across the patient groups and so dominate zoledronic acid. [redacted]

- Other solid tumours including lung cancer base case

The modelling that applies the AG NMA results in the following:

**Table 112 OST including lung AG NMA cost effectiveness results**

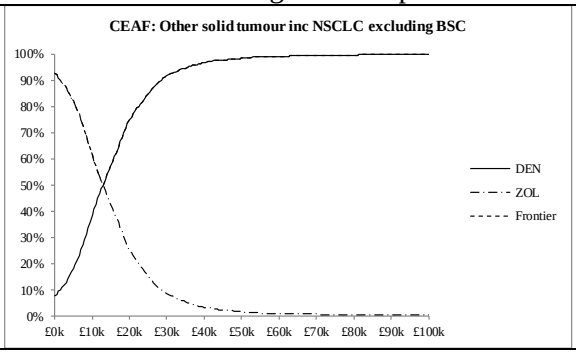
| **All Patients** | SREs | net | QALYs | net | Tx Costs | net | All Costs | net | ICER |
|---|---|---|---|---|---|---|---|---|---|
| BSC | 1.609 | -0.274 | 0.702 | 0.013 | [redacted] | | [redacted] | £2,573 | £197,550 |
| inc PAS | | | | | | | | £1,791 | £137,535 |
| Zol. Acid | 1.400 | -0.064 | 0.708 | 0.008 | [redacted] | | [redacted] | £880 | £115,741 |
| inc PAS | | | | | | | | £99 | £12,969 |
| Denosumab | 1.336 | .. | 0.715 | | [redacted] | | [redacted] | | |
| inc PAS | | | | | [redacted] | | [redacted] | | |
| **SRE Naive** | SREs | net | QALYs | net | Tx Costs | net | All Costs | net | ICER |
| BSC | 1.651 | -0.336 | 0.711 | 0.020 | [redacted] | | [redacted] | £2,482 | £125,301 |
| inc PAS | | | | | | | | £1,700 | £85,843 |
| Zol. Acid | 1.374 | -0.059 | 0.723 | 0.008 | [redacted] | | [redacted] | £892 | £113,054 |
| inc PAS | | | | | | | | £110 | £13,931 |
| Denosumab | 1.315 | .. | 0.731 | | [redacted] | | [redacted] | | |
| inc PAS | | | | | [redacted] | | [redacted] | | |
| **SRE Exper** | SREs | net | QALYs | net | Tx Costs | net | All Costs | net | ICER |
| BSC | 1.563 | -0.206 | 0.693 | 0.006 | [redacted] | | [redacted] | £2,671 | £470,820 |
| inc PAS | | | | | | | | £1,890 | £333,055 |
| Zol. Acid | 1.428 | -0.070 | 0.691 | 0.007 | [redacted] | | [redacted] | £868 | £118,884 |
| inc PAS | | | | | | | | £86 | £11,844 |
| Denosumab | 1.358 | .. | 0.699 | | [redacted] | | [redacted] | | |
| inc PAS | | | | | [redacted] | | [redacted] | | |

For other solid tumours including lung, possibly due to around 40% having lung cancer with the associated poor survival, the additional patient benefits from denosumab over zoledronic acid are muted: between 0.007 QALYs for SRE experienced patients and 0.008 QALYs for SRE naive patients. Without the PAS the additional cost of around £880 results in cost effectiveness estimates of more than £100k per QALY. [redacted] This results in an additional average cost of around £100 and cost effectiveness estimates of between £11,800 per QALY and £13,900 per QALY. Probabilistic modelling is again in line with this, an average gain of 0.008 QALYs at an additional average cost of £101 resulting in a central estimate of £13,200 per QALY across all patients. As would be anticipated given the preceding analysis, for those contraindicated to bisphosphonates, even with the PAS denosumab is not estimated to be cost effective against BSC. Across all patients the probabilistic modelling suggests similar central estimates of 0.013 QALYs and a net cost of £1,791 to yield a cost effectiveness estimate of £134,912 per QALY compared to BSC.

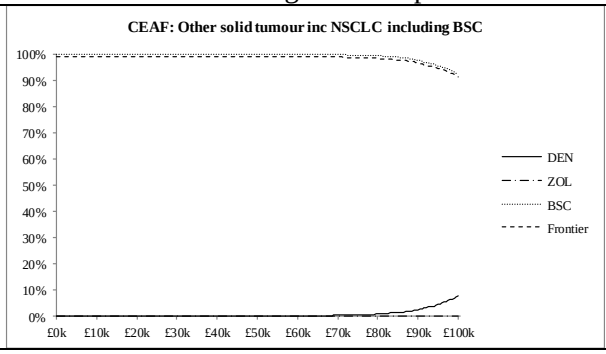
Note the apparently perverse impact among SRE experienced patients, in that denosumab is estimated to result in a smaller gain against BSC than against zoledronic acid. This is likely to have arisen from BSC being assumed not to be associated with any SAEs. This may be a reasonable approximation when there are clear differences in SRE rates between BSC and the active treatments. But it may not be so reasonable when differences are very small, and SAEs may come more to the fore.

**Figure 15 OST+Lung cancer CEAFs including the PAS**

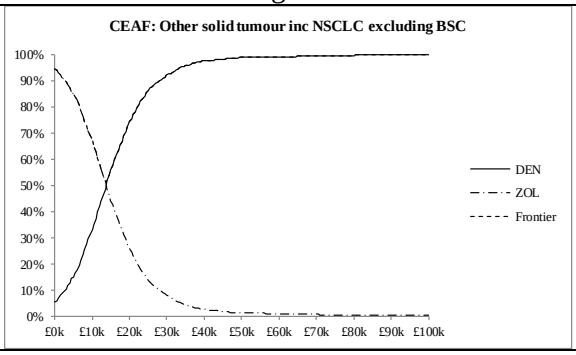
CEAF excluding BSC: all patients



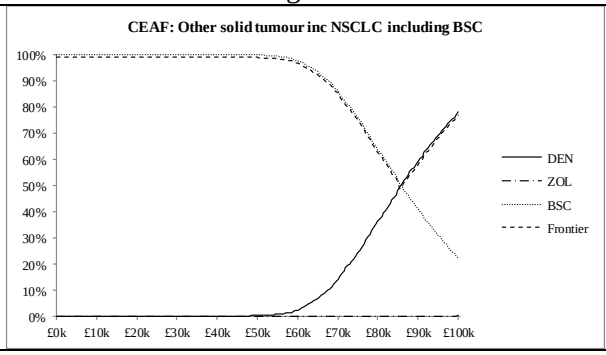

CEAF including BSC: all patients



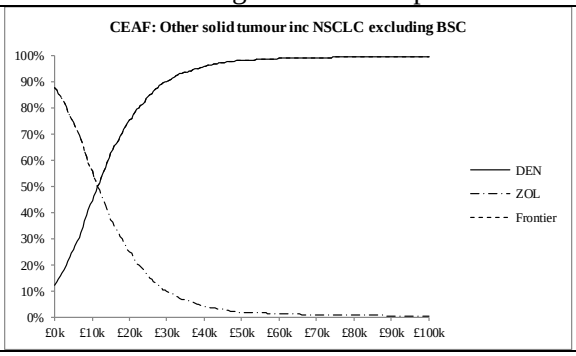

CEAF excluding BSC: SRE naive



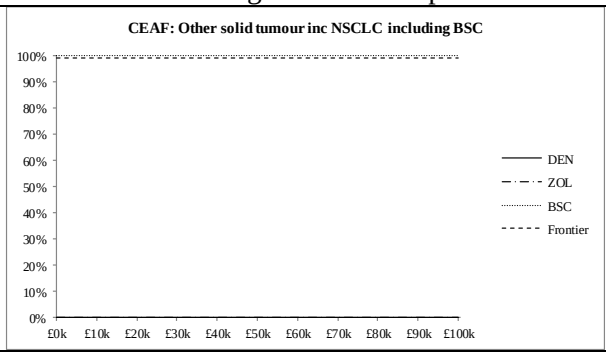

CEAF including BSC: SRE naive




CEAF excluding BSC: SRE experienced




CEAF including BSC: SRE experienced




- Other solid tumours including lung cancer sensitivity analyses

The univariate sensitivity analyses for the SRE experienced patient modelling for the cost effectiveness of denosumab are presented below.

**Table 113 OST + lung cancer univariate sensitivity analyses: All patients and SRE experienced patients**

| | SRE naïve patients vs BSC | | | | | | SRE experienced patients vs zoledronic acid | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Ex PAS | Inc PAS | SREs | QALYs | ICER ex | ICER inc | Ex PAS | Inc PAS | SREs | QALYs | ICER ex | ICER inc |
| Base Case | £2,482 | £1,700 | -0.336 | 0.020 | £125,301 | £85,843 | £868 | £86 | -0.070 | 0.007 | £118,884 | £11,844 |
| Amgen STARs | £2,416 | £1,634 | -0.336 | 0.020 | £121,955 | £82,497 | £836 | £54 | -0.070 | 0.007 | £114,502 | £7,462 |
| Amgen NMA | £2,509 | £1,727 | -0.320 | 0.018 | £136,091 | £93,688 | £849 | £68 | -0.081 | 0.008 | £108,102 | £8,605 |
| Amgen STARs+NMA | £2,447 | £1,665 | -0.320 | 0.018 | £132,743 | £90,340 | £814 | £33 | -0.081 | 0.008 | £103,640 | £4,142 |
| No naive util step | £2,482 | £1,700 | -0.336 | 0.014 | £176,138 | £120,670 | £868 | £86 | -0.070 | 0.007 | £118,884 | £11,844 |
| SCC ongoing mean | £2,482 | £1,700 | -0.336 | 0.023 | £108,030 | £74,010 | £868 | £86 | -0.070 | 0.008 | £108,309 | £10,790 |
| SCC ongoing max | £2,482 | £1,700 | -0.336 | 0.026 | £96,870 | £66,365 | £868 | £86 | -0.070 | 0.009 | £100,815 | £10,044 |
| No gen. mortality | £2,482 | £1,700 | -0.336 | 0.020 | £125,301 | £85,843 | £868 | £86 | -0.070 | 0.007 | £118,884 | £11,844 |
| 5 year horizon | £2,483 | £1,702 | -0.333 | 0.020 | £122,056 | £83,682 | £866 | £85 | -0.070 | 0.007 | £131,459 | £12,931 |
| 2 year horizon | £2,384 | £1,639 | -0.311 | 0.020 | £121,313 | £83,382 | £807 | £62 | -0.065 | 0.005 | £160,294 | £12,223 |
| vd Hout utility | £2,482 | £1,700 | -0.336 | 0.016 | £151,135 | £103,541 | £868 | £86 | -0.070 | 0.006 | £144,378 | £14,384 |
| No SAE P1+ | £2,482 | £1,700 | -0.336 | 0.024 | £105,093 | £71,998 | £868 | £86 | -0.070 | 0.004 | £233,090 | £23,221 |
| No SAE | £2,468 | £1,681 | -0.339 | 0.025 | £100,630 | £68,518 | £866 | £79 | -0.071 | 0.004 | £245,422 | £22,310 |
| No gen. discs. | £5,940 | £4,110 | -0.729 | 0.036 | £163,359 | £113,021 | £1,672 | -£158 | -0.145 | 0.020 | £82,035 | Dominant |
| No discs. | £6,087 | £4,213 | -0.744 | 0.037 | £164,845 | £114,086 | £1,740 | -£134 | -0.152 | 0.021 | £83,420 | Dominant |
| TTF form AG all | £2,481 | £1,699 | -0.334 | 0.020 | £123,772 | £84,770 | £868 | £86 | -0.070 | 0.007 | £118,884 | £11,844 |

In the above, the main sensitivities are to the source of the clinical effectiveness data and the treatment of SAEs and discontinuations. The manufacturer NMA increases the anticipated benefits within the all patient modelling by up to around 20%, with this mainly occurring among SRE naïve patients. Again, this is not unanticipated given the assessment group estimate for the HR for time to first SRE of 0.93 as compared to [redacted] from the manufacturer. The relative risk estimates for subsequent SREs are more similar at 0.87 and [redacted] respectively, and as a consequence the impact upon SRE patients is less.

[redacted] The slight increase in patient benefits is not sufficient to offset the increase in costs within the ex PAS scenario and the cost effectiveness worsens as a consequence. But with the PAS the balance alters and the SRE and SAE effects comes to the fore and the cost reductions result in cost effectiveness estimates with the PAS seeing denosumab come to dominate zoledronic acid. This is mirrored to a more muted extent by the sensitivity analysis which removes the impact of SAEs, causing the patient benefit to be reduced and cost effectiveness estimates to worsen accordingly.

While small in absolute terms, excluding SAEs has a reasonable percentage impact upon the anticipated patient gain compared to zoledronic acid and the ICER worsens considerably as a result. Partly as a consequence of this, removing discontinuations increases the modelled patient benefits though at some additional cost. As for the prostate cancer modelling, removing discontinuations tends to worsen the cost effectiveness for the comparison with BSC but improve it for the comparison with zoledronic acid.

A reduction in the price of zoledronic acid of 10% results in the cost effectiveness of denosumab compared to zoledronic acid for SRE experienced other solid tumours including lung cancer patients including the PAS [redacted].

Applying the head to head SRE naïve and SRE specific clinical effectiveness results for denosumab versus zoledronic acid, while retaining the remainder of the AG NMA results in the following.

**Table 114 OST including lung SRE patient subgroup effects cost effectiveness results**

| **All Patients** | SREs | net | QALYs | net | Tx Costs | net | All Costs | net | ICER |
|---|---|---|---|---|---|---|---|---|---|
| BSC | 1.609 | -0.269 | 0.702 | 0.014 | [redacted] | [redacted] | [redacted] | £2,584 | £189,354 |
| inc PAS | | | | | | [redacted] | | £1,803 | £132,081 |
| Zol. Acid | 1.400 | -0.060 | 0.708 | 0.008 | [redacted] | [redacted] | [redacted] | £892 | £108,347 |
| inc PAS | | | | | | [redacted] | | £110 | £13,364 |
| Denosumab | 1.340 | .. | 0.716 | | [redacted] | | [redacted] | | |
| inc PAS | | | | | [redacted] | | [redacted] | | |
| **SRE Naive** | SREs | net | QALYs | net | Tx Costs | net | All Costs | net | ICER |
| BSC | 1.651 | -0.377 | 0.711 | 0.023 | [redacted] | [redacted] | [redacted] | £2,419 | £103,064 |
| inc PAS | | | | | | [redacted] | | £1,638 | £69,766 |
| Zol. Acid | 1.374 | -0.100 | 0.723 | 0.012 | [redacted] | [redacted] | [redacted] | £829 | £71,747 |
| inc PAS | | | | | | [redacted] | | £47 | £4,076 |
| Denosumab | 1.274 | .. | 0.734 | | [redacted] | | [redacted] | | |
| inc PAS | | | | | [redacted] | | [redacted] | | |
| **SRE Exper** | SREs | net | QALYs | net | Tx Costs | net | All Costs | net | ICER |
| BSC | 1.563 | -0.152 | 0.693 | 0.003 | [redacted] | [redacted] | [redacted] | £2,763 | £920,203 |
| inc PAS | | | | | | [redacted] | | £1,981 | £659,874 |
| Zol. Acid | 1.428 | -0.016 | 0.691 | 0.005 | [redacted] | [redacted] | [redacted] | £960 | £207,239 |
| inc PAS | | | | | | [redacted] | | £178 | £38,458 |
| Denosumab | 1.411 | .. | 0.696 | | [redacted] | | [redacted] | | |
| inc PAS | | | | | [redacted] | | [redacted] | | |

The SRE subgroup specific clinical effectiveness estimates have the most dramatic impact upon this group of cancers. Possibly due to the short life expectancy and the limited time for an SRE naïve patient to experience their first SRE let alone their second, the better clinical effectiveness estimate for SRE naïve patients increases the estimated patient benefits by around 50% when compared to zoledronic acid. With the PAS this results in a cost effectiveness of only £4,076 per QALY, but unfortunately for this patient group the cost effectiveness against BSC remains poor: £69,766 per QALY. The effectiveness estimate for the SRE experienced sub-group is that denosumab is not much better than zoledronic acid, and even with the PAS the cost effectiveness estimate worsens to £38,458 per QALY.

- Lung cancer base case

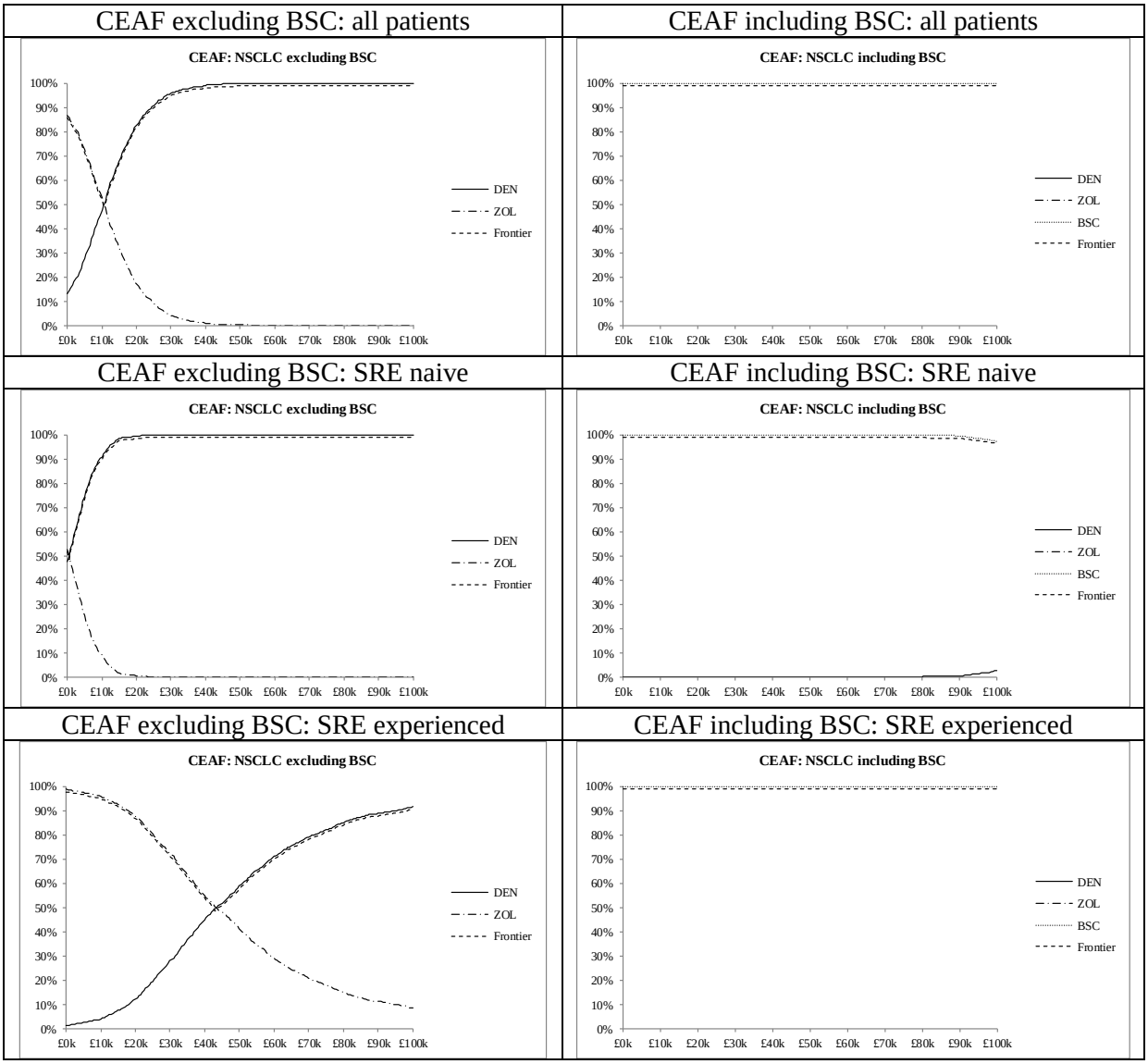
**Table 115 Lung cancer AG NMA cost effectiveness results**

| **All Patients** | SREs | net | QALYs | net | Tx Costs | net | All Costs | net | ICER |
|---|---|---|---|---|---|---|---|---|---|
| BSC | 0.928 | -0.187 | 0.443 | 0.009 | [redacted] | [redacted] | [redacted] | £2,317 | £263,132 |
| inc PAS | | | | | | [redacted] | | £1,637 | £185,966 |
| Zol. Acid | 0.800 | -0.059 | 0.446 | 0.006 | [redacted] | [redacted] | [redacted] | £738 | £127,599 |
| inc PAS | | | | | | [redacted] | | £58 | £10,099 |
| Denosumab | 0.741 | .. | 0.452 | | [redacted] | | [redacted] | | |
| inc PAS | | | | | [redacted] | | [redacted] | | |
| **SRE Naive** | SREs | net | QALYs | net | Tx Costs | net | All Costs | net | ICER |
| BSC | 0.849 | -0.207 | 0.458 | 0.012 | [redacted] | [redacted] | [redacted] | £2,292 | £198,073 |
| inc PAS | | | | | | [redacted] | | £1,613 | £139,364 |
| Zol. Acid | 0.736 | -0.095 | 0.461 | 0.009 | [redacted] | [redacted] | [redacted] | £683 | £79,694 |
| inc PAS | | | | | | [redacted] | | £3 | £382 |
| Denosumab | 0.642 | .. | 0.470 | | [redacted] | | [redacted] | | |
| inc PAS | | | | | [redacted] | | [redacted] | | |
| **SRE Exper** | SREs | net | QALYs | net | Tx Costs | net | All Costs | net | ICER |
| BSC | 1.015 | -0.165 | 0.427 | 0.006 | [redacted] | [redacted] | [redacted] | £2,343 | £403,622 |
| inc PAS | | | | | | [redacted] | | £1,664 | £286,598 |
| Zol. Acid | 0.870 | -0.021 | 0.430 | 0.003 | [redacted] | [redacted] | [redacted] | £798 | £288,320 |
| inc PAS | | | | | | [redacted] | | £118 | £42,698 |
| Denosumab | 0.849 | .. | 0.433 | | [redacted] | | [redacted] | | |
| inc PAS | | | | | [redacted] | | [redacted] | | |

The results for lung cancer are broadly similar to the previous analysis. For the comparison with zoledronic acid patient benefits are muted among SRE experienced patients: 0.003 QALYs. This may be a factor of their short life expectancy, but with the PAS the additional costs of £118 result in a cost effectiveness estimate of £42,698. The reverse applies to the SRE naïve subgroup where larger gains of 0.009 QALYs are achieved at minimal additional cost once the PAS is included. But the cost effectiveness for these patients compared to BSC remains poor at an estimated £139,364 per QALY.

As for the other analyses, the probabilistic modelling central estimates are broadly in line with those of the deterministic analysis. Across all patients the central estimate is of a 0.006 QALY gain compared to zoledronic acid and a 0.009 QALY gain compared to BSC. This is at an additional net cost central estimate of £1,640 and £61 with the PAS respectively.

**Figure 16 Lung cancer CEAFs including the PAS**




- Lung cancer sensitivity analyses

The univariate sensitivity analyses for the SRE experienced patient modelling for the cost effectiveness of denosumab compared to zoledronic acid is presented below.

**Table 116 Lung cancer univariate sensitivity analyses: All patients and SRE experienced patients**

| | SRE naïve patients vs BSC | | | | | | SRE experienced patients vs zoledronic acid | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Ex PAS | Inc PAS | SREs | QALYs | ICER ex | ICER inc | Ex PAS | Inc PAS | SREs | QALYs | ICER ex | ICER inc |
| Base Case | £2,292 | £1,613 | -0.207 | 0.012 | £198,073 | £139,364 | £798 | £118 | -0.021 | 0.003 | £288,320 | £42,698 |
| Amgen STARs | £2,257 | £1,578 | -0.207 | 0.012 | £195,059 | £136,350 | £780 | £101 | -0.021 | 0.003 | £282,094 | £36,472 |
| No naive util step | £2,292 | £1,613 | -0.207 | 0.009 | £262,474 | £184,677 | £798 | £118 | -0.021 | 0.003 | £288,320 | £42,698 |
| SCC ongoing mean | £2,292 | £1,613 | -0.207 | 0.012 | £185,758 | £130,700 | £798 | £118 | -0.021 | 0.003 | £280,207 | £41,496 |
| SCC ongoing max | £2,292 | £1,613 | -0.207 | 0.013 | £176,583 | £124,244 | £798 | £118 | -0.021 | 0.003 | £273,769 | £40,543 |
| No gen. mortality | £2,292 | £1,613 | -0.207 | 0.012 | £198,073 | £139,364 | £798 | £118 | -0.021 | 0.003 | £288,320 | £42,698 |
| 5 year horizon | £2,292 | £1,613 | -0.207 | 0.012 | £198,129 | £139,410 | £797 | £118 | -0.021 | 0.003 | £289,355 | £42,842 |
| 2 year horizon | £2,261 | £1,594 | -0.197 | 0.011 | £201,933 | £142,328 | £777 | £110 | -0.020 | 0.002 | £327,636 | £46,221 |
| vd Hout utility | £2,292 | £1,613 | -0.207 | 0.009 | £256,735 | £180,639 | £798 | £118 | -0.021 | 0.002 | £373,106 | £55,254 |
| No SAE P1+ | £2,292 | £1,613 | -0.207 | 0.013 | £174,867 | £123,037 | £798 | £118 | -0.021 | 0.001 | £651,537 | £96,487 |
| No SAE | £2,278 | £1,595 | -0.208 | 0.014 | £164,993 | £115,483 | £794 | £111 | -0.021 | 0.001 | £776,986 | £108,380 |
| No gen. discs. | £3,949 | £2,802 | -0.304 | 0.016 | £252,990 | £179,472 | £1,177 | £30 | -0.018 | 0.004 | £270,020 | £6,782 |
| No discs. | £3,991 | £2,831 | -0.307 | 0.016 | £254,158 | £180,325 | £1,196 | £37 | -0.019 | 0.004 | £270,522 | £8,387 |

For the comparison with zoledronic acid among SRE experienced patients, the number of SREs avoided and the patient gains anticipated by the base case are extremely muted. Given the relative risk for subsequent SREs of 0.97 as estimated within the AG NMA it appears that results within among SRE experienced patients may be being driven at least in part by the rates of SAEs. The sensitivity analyses for lung cancer that remove the discontinuations have a similar impact as within the OST+lung modelling, given that in the absence of other data the lung cancer modelling assumes the adverse event rates and discontinuations of the OST + lung modelling.

Results are more predictable and stable among the SRE naïve patients, given the hazard ratio for time to first SRE among SRE naïve patients of 0.79 for denosumab compared to zoledronic acid and of 0.86 for zoledronic acid compared to placebo. The main sensitivities are in the treatment of utilities, with the removal of the step change going from naïve to experienced reducing patient benefits by around one third. Given the short life expectancy, the application of the van den Hout utility modifiers also has quite a large impact and also causes the patient benefits to be reduced by around one third.

A reduction in the price of zoledronic acid of 10% results in the cost effectiveness of denosumab compared to zoledronic acid for SRE experienced other solid tumours including lung cancer patients including the PAS [redacted].

*Sensitivity analyses*

The sensitivity analyses are presented in greater detail within each of the cancer specific modelling sections above.

In brief, the results of the assessment group for breast cancer are broadly in line with those of the manufacturer. There is some sensitivity in results to the rates of SAEs due to the higher rate of renal toxicity applied within the zoledronic acid arm. Discontinuations tend to increase net costs compared to zoledronic acid broadly in line with the net benefits and the cost effectiveness estimates are reasonably stable. Applying the SRE naïve and SRE experienced specific hazard ratios and relative risks has only a muted impact.

For prostate cancer the assessment group base case results are again broadly in line with those of the manufacturer. Results show some sensitivity to the utility decrements from spinal cord compression being extended to the end of life. Applying the SRE naïve and SRE experienced specific hazard ratios and relative risks has a more noticeable effect. Among the SRE experienced patients this sees the net impact of denosumab compared to zoledronic acid fall from a reduction in SREs of 0.290 to a reduction of only 0.088, with a parallel impact upon the anticipated patient benefits.

Within the modelling of other solid tumours including lung, the base case number of SREs avoided from denosumab compared to zoledronic acid for SRE experienced patients is reasonably sensitive to whether the assessment group NMA results are applied or the manufacturer NMA results. But whichever is applied the number of SREs avoided through use of denosumab over zoledronic acid is small and results become sensitive to the other parameters within the modelling, notable rates of SAEs and discontinuation rates. Results for denosumab compared to best supportive care are more stable as the analysis is driven more by the relative rates of SREs, particularly among SRE naïve patients.

Applying the SRE naïve and SRE experienced specific hazard ratios and relative risks has a relatively large impact upon results for the SRE experienced other solid tumours including lung modelling. This may in itself be sufficient to render denosumab, even with the PAS, not cost effective compared to zoledronic acid for this group.

The above is further mirrored in the modelling of lung cancer, where the base case number of SREs avoided from denosumab compared to zoledronic acid for SRE experienced patients is very small given the relative risk of 0.97 for subsequent SREs. In the light of the anticipated patient gains are small, and the cost effectiveness estimates are volatile to the input values for other model parameters such as SAEs and discontinuation rates. Results for denosumab compared to best supportive care are again more stable, and again this is particularly the case for SRE naïve patients for whom the relative risk for denosumab compared to zoledronic acid is 0.79 and for zoledronic acid compared to BSC is 0.86.

An aspect that may have an impact beyond that modelled is the treatment of spinal cord compressions. Extending the average quality of life decrement measured in the five months subsequent to the compression through to death improves the estimated cost effectiveness, particularly among SRE naïve prostate cancer patients. There remains uncertainty as to the rate of paralysis from spinal cord compression, the long terms quality of life impacts from spinal cord compression and the needs for long term care together with the associated costs.

Where the appropriate comparator is zoledronic acid, there is additional uncertainty concerning its likely price when it shortly comes off patent. [redacted]

Probabilistic modelling suggests that within the usual range of cost effectiveness thresholds there is relatively little uncertainty around the cost effectiveness acceptability frontier. The central estimates are also in line with those of the deterministic analyses.

*Discussion*

For ease of reference, the manufacturer base case results, the ERG base case results and the ERG structural sensitivity analyses that apply the SRE naïve and SRE experienced specific HRs and RRs are summarised below for the comparison with zoledronic acid and the comparison with BSC.

**Table 117 Summary of results denosumab versus zoledronic acid**

| | | Breast cancer | | Prostate cancer | | OST+Lung | | Lung cancer | |
|---|---|---|---|---|---|---|---|---|---|
| | | **ex PAS** | **inc PAS** | **ex PAS** | **inc PAS** | **ex PAS** | **inc PAS** | **ex PAS** | **inc PAS** |
| Manufacturer: pooled RR&HR | | | | | | | | | |
| All | Δ Cost | £1,484 | -£483 | | | | | | |
| | Δ QALY | 0.007 | | | | | | | |
| | ICER | £203,387 | dominant | | | | | | |
| Exper. | Δ Cost | | | £922 | -£281 | £757 | -£43 | | |
| | Δ QALY | | | 0.006 | | 0.004 | | | |
| | ICER | | | £157,276 | dominant | £205,580 | dominant | | |
| AG modelling: pooled RR&HR | | | | | | | | | |
| All | Δ Cost | £1,680 | -£270 | £941 | -£243 | £880 | £99 | £738 | £58 |
| | Δ QALY | 0.013 | | 0.020 | | 0.008 | | 0.006 | |
| | ICER | £126,821 | dominant | £46,976 | dominant | £115,741 | £12,969 | £127,599 | £10,099 |
| Naive | Δ Cost | £1,725 | -£225 | £897 | -£287 | £892 | £110 | £683 | £3 |
| | Δ QALY | 0.015 | | 0.025 | | 0.008 | | 0.009 | |
| | ICER | £117,186 | dominant | £35,732 | dominant | £113,054 | £13,931 | £79,694 | £382 |
| Exper. | Δ Cost | £1,615 | -£335 | £1,016 | -£123 | £868 | £86 | £798 | £118 |
| | Δ QALY | 0.011 | | 0.006 | | 0.007 | | 0.003 | |
| | ICER | £145,171 | dominant | £167,503 | dominant | £118,884 | £11,844 | £288,320 | £42,698 |
| AG modelling: SRE naïve and SRE experienced specific HRs+RRs | | | | | | | | | |
| All | Δ Cost | £1,691 | -£259 | £1,078 | -£107 | £892 | £110 | | |
| | Δ QALY | 0.012 | | 0.010 | | 0.008 | | | |
| | ICER | £137,625 | dominant | £113,237 | dominant | £108,347 | £13,364 | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Naive | Δ Cost | £1,760 | -£190 | £1,066 | -£118 | £829 | £47 | | |
| | Δ QALY | 0.013 | | 0.011 | | 0.012 | | | |
| | ICER | £136,390 | dominant | £93,575 | dominant | £71,747 | £4,076 | | |
| Exper. | Δ Cost | £1,592 | -£358 | £1,109 | -£76 | £960 | £178 | | |
| | Δ QALY | 0.011 | | 0.004 | | 0.005 | | | |
| | ICER | £139,635 | dominant | £249,575 | dominant | £207,238 | £38,458 | | |

**Table 118 Summary of results denosumab versus BSC**

| | | Breast cancer | | Prostate cancer | | OST+Lung | | Lung cancer | |
|---|---|---|---|---|---|---|---|---|---|
| | | **ex PAS** | **inc PAS** | **ex PAS** | **inc PAS** | **ex PAS** | **inc PAS** | **ex PAS** | **inc PAS** |
| Manufacturer: pooled RR&HR | | | | | | | | | |
| Exper. | Δ Cost | | | £3,993 | £2,790 | £2,530 | £1,730 | | |
| | Δ QALY | | | 0.039 | | 0.021 | | | |
| | ICER | | | £102,067 | £71,320 | £122,499 | £83,763 | | |
| AG modelling: pooled RR&HR | | | | | | | | | |
| All | Δ Cost | £6,114 | £4,165 | £3,880 | £2,695 | £2,573 | £1,791 | £2,317 | £1,637 |
| | Δ QALY | 0.027 | | 0.030 | | 0.013 | | 0.009 | |
| | ICER | £224,411 | £152,847 | £130,674 | £90,788 | £197,550 | £137,535 | £263,132 | £185,966 |
| Naive | Δ Cost | £6,223 | £4,273 | £3,832 | £2,648 | £2,482 | £1,700 | £2,292 | £1,613 |
| | Δ QALY | 0.034 | | 0.038 | | 0.020 | | 0.012 | |
| | ICER | £181,007 | £124,291 | £100,601 | £69,510 | £125,301 | £85,843 | £198,073 | £139,364 |
| Exper. | Δ Cost | £5,958 | £4,008 | £4,009 | £2,825 | £2,671 | £1,890 | £2,343 | £1,664 |
| | Δ QALY | 0.017 | | 0.007 | | 0.006 | | 0.006 | |
| | ICER | £350,856 | £236,037 | £574,364 | £404,707 | £470,820 | £333,055 | £403,622 | £286,598 |
| AG modelling: SRE naïve and SRE experienced specific HRs+RRs | | | | | | | | | |
| All | Δ Cost | £6,126 | £4,176 | £4,016 | £2,832 | £2,584 | £1,803 | | |
| | Δ QALY | 0.026 | | 0.019 | | 0.014 | | | |
| | ICER | £233,015 | £158,844 | £209,541 | £147,750 | £189,354 | £132,081 | | |
| Naive | Δ Cost | £6,258 | £4,308 | £4,001 | £2,816 | £2,419 | £1,638 | | |
| | Δ QALY | 0.033 | | 0.024 | | 0.023 | | | |
| | ICER | £192,177 | £132,297 | £164,155 | £115,564 | £103,064 | £60,766 | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Exper. | Δ Cost | £5,936 | £3,986 | £4,057 | £2,873 | £2,763 | £1,981 | | |
| | Δ QALY | 0.017 | | 0.005 | | 0.003 | | | |
| | ICER | £343,887 | £230,917 | £797,197 | £564,495 | £920,203 | £659,874 | | |

The manufacturer case is broadly that while the average patient benefits from the reduced number of SREs is not large, with the PAS denosumab will be cost saving compared to zoledronic acid. [redacted] As a consequence, denosumab is estimated to dominate zoledronic acid among patients for whom zoledronic acid is indicated when the PAS is included.

But for patients for whom zoledronic acid is not indicated, the manufacturer accepts that even with the PAS the relatively small patient gains do not justify the additional cost of denosumab. Manufacturer cost effectiveness estimates for denosumab compared to BSC are typically in excess of £100k per QALY, and even with the PAS are closer to £100k per QALY than £50k per QALY.

AG within trial analyses suggest that for breast cancer patients denosumab results in a slightly lower average number of SREs compared to zoledronic acid, and that this will translate into a small average annual gain of perhaps 0.003 to 0.006 QALYs: roughly equivalent to one to two additional days in full health or two to three days at the SRE naïve average quality of life. Without the PAS the additional cost of denosumab does not justify these relatively minor gains. With the PAS denosumab is estimated to be broadly cost neutral to slightly cost saving, and so cost effective compared to zoledronic acid. [redacted]

Within trial analyses suggest that for prostate cancer patients denosumab results in a slightly lower average number of SREs compared to zoledronic acid. This translates into a slightly larger additional average annual gain of perhaps 0.008 to 0.016 QALYs. The reason for this difference in prostate cancer is the greater proportion of spinal cord compressions within the overall number of SREs. [redacted] This aspect is not considered in either the manufacturer model or the AG economic model.

Without the PAS the additional cost of denosumab still does not justify the relatively minor estimated gains. With the PAS, [redacted] denosumab is estimated as to increase annual costs by around £100 which translates into cost effectiveness estimates of between £6,545 per QALY and £15,272 per QALY. But this AG within trial analysis does not distinguish between SRE naïve and SRE experienced patients.

Given the slightly larger patient gains estimated for prostate cancer patients from denosumab, its cost effectiveness compared with zoledronic acid is not as sensitive to the price of zoledronic acid as breast cancer. [redacted]

For the cost utility modelling within breast cancer, the lifetime gains across all patients are estimated to be around 0.013 QALYs. This is again small, and does not justify the additional cost of £1,691 per patient compared to zoledronic acid. With the PAS [redacted] denosumab is estimated to dominate zoledronic acid. But for those contraindicated to bisphosphonates the cost effectiveness is poor: even with the PAS the cost effectiveness is £158,844 per QALY. Applying the SRE naïve and SRE experienced subgroup specific clinical effectiveness has little impact upon the results, as these estimates are reasonably close to the pooled all patient estimates.

For the cost utility modelling within prostate cancer, across all patients the gain from denosumab over zoledronic acid is around 0.020 QALYs while compared to BSC it is 0.030 QALYs, at net costs without the PAS of £941 and £3,880 respectively. Without the PAS, compared to zoledronic acid this results in a cost effectiveness of £46,976 per QALY. Cost effectiveness is estimated to be slightly better among the SRE naïve at £35,732 per QALY, but the quid pro quo is a worse cost effectiveness among the SRE experienced of £167,503 per QALY. This may arise in large part due to the estimated step change in HRQoL arising from a patient's first SRE.

With the PAS, denosumab is estimated to be cost saving compared to zoledronic acid and so dominate it. For those contraindicated to bisphosphonates, denosumab is not estimated to be cost effective compared to BSC.

Applying the SRE naïve and SRE experienced subgroup specific clinical effectiveness has a reasonably large impact upon the results. The impact of this on the modelling is not symmetric. As the model progresses, more patients fall into the SRE experienced group and as a consequence the estimated cost effectiveness of denosumab worsens. But the PAS is still sufficient for [redacted] denosumab being estimated to remain dominant over zoledronic acid.

Within the cost utility modelling of other solid tumours including lung, the gains from denosumab over zoledronic acid are estimated to be less than 0.01 QALYs. Without the PAS denosumab is not cost effective, but with it the small additional overall costs of around £100 result in cost effectiveness estimates of between £11,800 per QALY and £13,900 per QALY. The impact of applying the SRE subgroup specific estimates within this group is quite large. While it improves the estimates cost

effectiveness of denosumab compared to BSC for SRE naïve patients, even with the PAS it is not sufficient to render it cost effective. [redacted], the cost effectiveness estimate for denosumab worsens to £38,458 per QALY compared to zoledronic acid among these patients.

For lung cancer, possibly due to the short life expectancy the patient gains from denosumab over zoledronic acid among SRE experienced patients are estimated to be small: 0.003 QALYs. Even with the PAS, the additional cost of £118 results in a cost effectiveness of £42,698 per QALY.

Some questions for possible consideration are:

- To what extent does the available data on SRE naïve patients and SRE experienced patients reflect the likely patient groups for whom zoledronic acid is used? 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?
- Should the base case apply the SRE subgroup specific clinical effectiveness estimates? This has little impact within breast cancer. But it has quite large, adverse effects upon the cost effectiveness of denosumab for SRE experienced patients in prostate cancer and other solid tumours including lung.
- 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 zoledronic acid would be sufficient to make denosumab not cost effective when judged by conventional thresholds.

## 12 ASSESSMENT OF FACTORS RELEVANT TO THE NHS AND OTHER PARTIES

Any change in the treatment pathway of bone metastases is likely to have an impact on the NHS and other parties. The impact of denosumab depends on whether the patient would alternatively have received an intravenous (IV) bisphosphonate (BP), oral BP or best supportive care (BSC).

### 12.1 Factors relevant to the NHS

For patients who would have received an IV bisphosphonate, subcutaneous denosumab is advantageous. Firstly, subcutaneous administration does not require inpatient administration. Denosumab could be given in an outpatient setting, GP surgery or even potentially at home by a district nurse or other qualified healthcare provider. Compared to intravenous injections, subcutaneous administration requires a shorter time to administer, is associated with few complications and is technically easier. This is not relevant to those patients who would have been prescribed an oral bisphosphonate or who need to attend hospital for other reasons, such as IV chemotherapy. Any shift of care from acute hospitals into the community has implications for the NHS. Additional resources and training may be needed in the community. Denosumab is administered using the standard subcutaneous method. NHS staff need to be aware that in prostate cancer and other solid tumours bisphosphonates may be used for treatment of bone pain when conventional analgesics have failed. Denosumab is licensed for the prevention of skeletal related events and not the treatment of bone pain. It is conceivable that reduction in pain is a method of preventing the need for radiotherapy. However evidence for the analgesic effects of denosumab is not consistent. Prescribers would also need to be aware of the potential adverse events, such as hypocalcaemia and osteonecrosis of the jaw.

Secondly for patients who are prescribed oral bisphosphonates adherence may increase if they are switched to denosumab. Oral bisphosphonates are inconvenient for patients to take because of side effects and the required technique. Subcutaneous injection avoids these unpleasant upper gastrointestinal side effects. However, it should be noted that according to the Xgeva SPC the diarrhoeal adverse events are “very common”.

For those patients who would have otherwise been treated with best supportive care, administration of denosumab would require additional resources. Denosumab requires storage at 2°C-8°C in a refrigerator. Most NHS premises have facilities to store medicinal products in a refrigerator. However if any premises did not have these facilities or required more space additional resources may be necessary.

Bisphosphonates require renal monitoring. This has resource issues, but also safety issues. Any medication which requires dose adjustment according to renal function increases the likelihood of human error. Since denosumab is a fixed dose single injection the risk of human error is substantially

reduced. Denosumab may reduce the need for laboratory services. However patients with advanced cancer usually undergo frequent blood sampling, including measure of renal function.

### 12.2 Factors relevant to other parties

Delaying or preventing SREs may result in patients being mobile for longer. It should be noted that mobility has not been assessed in the pivotal trials. However preventing pathological fractures, surgery to bone or spinal cord compression is likely to result in reduced immobility. In turn this would reduce the burden on carers.

Patients who would have alternatively been prescribed an intravenous bisphosphonate may have reduced need for hospital attendance. Administration may be possible in the community. This would reduce travelling time for both patients and carers. This is particularly important for patients who have problems with mobility, live in rural locations or have poor transport links. In addition it may reduce the number of days off work for patients who are still employed or for carers who need to take time off to attend hospital appointments. For patients who are required to attend hospital, denosumab would shorten the time in hospital. Total time for administration of zoledronic acid may be 30-45 minutes depending on the time it takes to establish IV access, whereas a subcutaneous injection would only take a few minutes.

Subcutaneous administration may also be less unpleasant for many patients compared to IV or oral bisphosphonate administration.

For patients who would have previously been treated with best supportive care alone, the addition of denosumab would usually mean additional healthcare appointments. This may require the patient and carer travelling to an acute hospital or GP surgery.

# 13 DISCUSSION

## 13.1 Clinical effectiveness

### *13.1.1 Statement of principal findings*

*Breast cancer*

There was a statistically significant difference in favour of denosumab compared with zoledronic acid for the time to first on-study SRE for all patients (HR 0.82, 95% CI 0.71 to 0.95; not reached versus median 26.4 months) (Table 119) [redacted] (Table 119) [redacted] For both time to first on-study SRE, and risk of developing first-and-subsequent SREs, the distribution of type of SRE was similar across treatment groups, with pathological fracture ([redacted] and radiation to bone ([redacted] being the most common while there were few occurrences of spinal cord compression ([redacted] or surgery to bone ([redacted]).

For the subgroup of patients with no or mild pain at baseline, denosumab delayed the time to development of moderate or severe worst pain (worst pain score of > 4 points) compared with zoledronic acid ([redacted]). The median time to worsening pain (≥ 2 point increase from baseline) was slightly longer for denosumab (median [redacted] versus [redacted] months). In terms of quality of life, overall mean FACT scores remained similar between the groups, [redacted].

In terms of adverse events, there were more occurrences of hypocalcaemia in the denosumab group compared with the zoledronic acid group (5.5% versus 3.4%), rates of ONJ were slightly higher (2.0% versus 1.4%), while there were lower rates of events associated with renal impairment (4.9% versus 8.5%), acute phase reactions (10.4% versus 27.3%) or [redacted]. Overall survival was balanced between the denosumab and zoledronic acid groups (HR 0.95, 95% CI 0.81 to 1.11); median [redacted] months versus [redacted]).

In the Assessment Group's NMA, there was a statistically significant difference in favour of denosumab compared with zoledronic acid, pamidronate or placebo for both time to first on-study SRE and risk of first-and subsequent SREs (Table 120). [redacted]

*Prostate cancer*

There was a statistically significant difference in favour of denosumab compared with zoledronic acid for the time to first on-study SRE for all patients (HR 0.82, 95% CI 0.71 to 0.95; median 20.7 versus 17.1 months) (Table 119) and for those with no prior SRE (HR 0.80, 95% CI 0.67 to 0.95) [redacted] (Table 119) [redacted] For both time to first on-study SRE, and risk of first-and-subsequent SREs, the distribution of type of SRE was similar across treatment groups, with radiation to bone ([redacted]) and pathological fracture ([redacted] being the most common while there were fewer occurrences of spinal cord compression ([redacted] or surgery to bone ([redacted]

The time to development of moderate or severe worst pain, in patients with no/mild pain at baseline, favoured denosumab compared with zoledronic acid (median 5.8 versus 4.9 months) without being statistically significant (HR 0.89, 95% CI 0.77 to 1.04). The median time to worsening pain was similar (median [redacted] versus [redacted] months). In terms of quality of life, overall mean FACT scores remained similar between the groups, [redacted].

In terms of adverse events, there were more occurrences of hypocalcaemia in the denosumab group compared with the zoledronic acid group (12.8% versus 5.8%), slightly higher rates of ONJ (2.3% versus 1.3%) and [redacted], while events associated with renal impairment (14.7% versus 16.2%) and acute phase reactions (8.4% versus 17.8%) were lower. Overall survival was similar between the treatment groups (HR 1.03, 95% CI 0.91 to 1.17; median 19.4 versus 19.8 months).

The Assessment Group's NMA reported a statistically significant difference in favour of denosumab compared with zoledronic acid or placebo for both time to first on-study SRE and risk of first-and subsequent SREs, [redacted] (Table 120).

*Non-small cell lung cancer (NSCLC)*

For time to first-on-study SRE for all patients the difference favoured denosumab without being statistically significant (HR 0.84, 95% CI 0.64 to 1.10[redacted] (Table 120). There was a statistically significant difference in favour of denosumab for overall survival (HR 0.79, 95% CI 0.65 to 0.95). The following outcomes were not reported for

NSCLC: time to first on-study SRE or risk of first-and-subsequent SRE by prior history of SRE or type of SRE; pain scores or quality of life; hypercalcaemia, hypocalcaemia, ONJ, events associated with renal impairment or acute phase reactions.

The manufacturer's submission did not perform a NMA of NSCLC. In the Assessment Group's NMA, there was a statistically significant difference in favour of denosumab compared with placebo for both time to first on-study SRE and risk of first-and-subsequent SREs. In the comparison with zoledronic acid there was a statistically significant difference in favour of denosumab for time to first on-study SRE but not for risk of first-and-subsequent SREs, although the direction of effect favoured denosumab (Table 120).

*Other solid tumours (excluding NSCLC)*

There was a statistically significant difference in favour of denosumab for median time to first on-study SRE for all patients (HR 0.79, 95% CI 0.62 to 0.99; [redacted] (Table 119). Overall survival was similar (HR 1.08, 95% CI 0.90 to 1.30). The following outcomes were not reported for other solid tumours excluding NSCLC: time to first on-study SRE or risk of first-and-subsequent SREs by prior history of SRE or type of SRE; pain scores or quality of life; hypercalcaemia, hypocalcaemia, ONJ, events associated with renal impairment or acute phase reactions.

The manufacturer's submission did not perform a NMA of other solid tumours excluding NSCLC. In the Assessment Group's NMA there was a statistically significant difference in favour of denosumab compared with zoledronic acid or placebo for both time to first on-study SRE and risk of first-and subsequent on-study SREs (Table 120).

*Other solid tumours (including NSCLC)*

In the manufacturer's post hoc analysis (excluding multiple myeloma) there was a statistically significant difference in favour of denosumab for time to first on-study SRE for all patients ([redacted]) (Table 119) [redacted]

For risk of developing first-and-subsequent SREs, for all patients, the difference was borderline significant in favour of denosumab (RR 0.85, 95% CI 0.72 to 1.00) (Table 119), [redacted]. For both time to first on-study SRE, and risk of first-and-subsequent SREs, the distribution of type of SRE was similar across treatment groups, with radiation

to bone ([redacted]) and pathological fracture ([redacted]) being the most common while there were fewer occurrences of spinal cord compression ([redacted]) or surgery to bone ([redacted]).

Denosumab delayed the time to development of moderate or severe worst pain, in patients with no/mild pain at baseline, compared with zoledronic acid ([redacted]) and also the time to worsening pain (median [redacted] versus [redacted] months, p = 0.04). In terms of quality of life, overall mean FACT scores remained similar between the groups, [redacted].

In terms of adverse events, there were more occurrences of hypocalcaemia in the denosumab group compared with the zoledronic acid group (10.8% versus 5.8%), rates of [redacted] and ONJ (1.3% versus 1.1%) were similar, while there were lower rates of events associated with renal impairment (8.3% versus 10.9%) or acute phase reactions (6.9% versus 14.5%). Overall survival was similar (HR 0.92, 95% CI 0.81 to 1.05; median [redacted] versus [redacted] months).

The Assessment Group's NMA reported a statistically significant difference in favour of denosumab compared with zoledronic acid or placebo for both time to first on-study SRE and risk of first-and subsequent SREs, [redacted] (Table 120).

**Table 119 Time to first on-study SRE and time to first-and-subsequent on-study SRE for the denosumab RCTs**

| | Breast cancer (Study 136) | | Prostate cancer (Study 103) | | NSCLC (Study 244 subgroup) | | OST exc NSCLC (Study 244 subgroup) | | OST inc NSCLC (Study 244 post hoc analysis) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Dmab (n=1026) | Za (n=1020) | Dmab (n=950) | Za (n=951) | Dmab (n=350) | Za (n=352) | Dmab (n=449) | Za (n=445) | Dmab (n=800) | Za (n=797) |
| ***Time to first on-study SRE*** | | | | | | | | | | |
| **n (%)** | 315 (30.7) | 372 (36.5) | 341 (35.9) | 386 (40.6) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Median time, months** | NR | 26.4 | 20.7 | 17.1 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **HR (95% CI)** | 0.82 (0.71, 0.95) | | 0.82 (0.71, 0.95) | | 0.84 (0.64, 1.10) | | 0.79 (0.62, 0.99) | | [redacted] | |
| ***Risk of first-and-subsequent on-study SREs*** | | | | | | | | | | |
| **Number of events** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 328 | 374 |
| **Mean number of SREs per patient** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Rate ratio (95% CI)** | 0.77 (0.66, 0.89) | | 0.82 (0.71, 0.94) | | [redacted] | | [redacted] | | 0.85 (0.72, 1.00) | |

Source: manufacturer's submission and CSR 224.

**Notes:**

1. Dmab, denosumab; ZA, zoledronic acid; OST, other solid tumours; exc, excluding; NR, not reached.
2. Median time for NSCLC was reported as days ([redacted] for denosumab, [redacted] for zoledronic acid) and divided by 28 by the AG to convert to months.
3. Median time for OST was reported as [redacted] days for zoledronic acid and divided by 28 by the AG to convert to months.

**Table 120 Assessment Group and manufacturer NMA results for time to first on-study SRE and time to first-and-subsequent on-study SRE**

| Comparison | Time to first on-study SRE | | Time to first-and subsequent SRE | |
|---|---|---|---|---|
| | AG NMA HR (95% CI) | MS NMA HR (95% CI) | AG NMA RR (95% CI) | MS NMA RR (95% CI) |
| ***Breast cancer*** | | | | |
| **Dmab v Za** | 0.81 (0.78, 0.83) | [redacted] | 0.75 (0.73, 0.76) | [redacted] |
| **Dmab v pam** | 0.89 (0.86, 0.93) | [redacted] | 0.57 (0.55, 0.59) | [redacted] |
| **Dmab v placebo** | 0.48 (0.46, 0.51) | [redacted] | 0.42 (0.41, 0.43) | [redacted] |
| **Dmab v Ia** | Not done | [redacted] | Not done | [redacted] |
| ***Prostate cancer*** | | | | |
| **Dmab v Za** | 0.57 (0.54, 0.59) | [redacted] | 0.83 (0.81, 0.85) | [redacted] |
| **Dmab v placebo** | 0.45 (0.43, 0.48) | [redacted] | 0.56 (0.54, 0.58) | [redacted] |
| ***NSCLC*** | | | | |
| **Dmab v Za** | 0.79 (0.76, 0.81) | Not done | 0.97 (0.95, 1.01) | Not done |
| **Dmab v placebo** | 0.66 (0.63, 0.68) | Not done | 0.69 (0.66, 0.73) | Not done |
| ***OST excluding NSCLC*** | | | | |
| **Dmab v Za** | 0.93 (0.89, 0.96) | Not done | 0.82 (0.79, 0.84) | Not done |
| **Dmab v placebo** | 0.37 (0.35, 0.39) | Not done | 0.67 (0.64, 0.70) | Not done |
| ***OST including NSCLC*** | | | | |
| **Dmab v Za** | 0.93 (0.90, 0.96) | [redacted] | 0.87 (0.85, 0.89) | [redacted] |
| **Dmab v placebo** | 0.44 (0.42, 0.46) | [redacted] | 0.63 (0.61, 0.66) | [redacted] |

**Notes:**

1. AG, Assessment Group; MS, Manufacturer's submission; NMA, network meta-analysis; HR, hazard ratio; Za, zoledronic acid; pam, pamidronate; Ia, ibandronic acid.

### *13.1.2 Strengths and limitations of the assessment*

In terms of strengths, our review focused on RCTs, resulting in a high level of evidence. Where outcome data were not available from published reports we attempted to source such data from the manufacturer's submission and clinical study reports. We undertook a network meta-analysis in order to provide an indirect estimate of the effectiveness of denosumab against appropriate comparators that were not considered in the direct evidence. A NMA analysis of NSCLC and OST (excluding NSCLC) was undertaken which reduced the degree of methodological heterogeneity within the analysis. We did not assume a class effect for bisphosphonates and instead incorporated different types of bisphosphonate, as appropriate for the type of primary cancer being considered, in the network meta-analysis.

In terms of limitations, non-English language studies were excluded from the review due to the tight timelines. Fewer outcomes were available for non-small cell lung cancer, and other solid tumours excluding NSCLC, than were reported for breast cancer, prostate cancer or other solid tumours including NSCLC. Definitions used by the studies of what constituted BSC varied both within and across each of the primary tumour types. The study by Saad and colleagues[118] was used in the network meta-analysis for BSC. The control arm was randomised to receive placebo. Both groups received standard pain management, including analgesics, radiation or "other treatment" at the discretion of the clinician. This standard treatment is consistent with the best supportive care described by the AG clinical expert (RJ).

The strength of a network meta-analysis is that all the available and relevant evidence (direct and indirect) can be considered in a single consistent analysis. However, a key limitation of the NMA in this assessment is the small number of trials included. Furthermore, network meta-analyses are not randomised comparisons but rather observational findings across studies and therefore the results of are subject to considerable uncertainty and should be interpreted with caution.

### *13.1.3 Uncertainties*

*External validity of the denosumab RCTs*

The three denosumab RCTs were large, international, multi-centre trials. The participants all had advanced cancer (breast, prostate, lung or other solid tumours) with ≥ 1 bone metastases, ECOG status ≤ 2 and a life expectancy of ≥ 6 months. Therefore it is reasonable to expect that the results of the trials would be generalisable to patients meeting the above criteria. It is important to note that these results would not be generalisable to patients with a life expectancy of < 6 months. [redacted] It is unclear to what extent, if any, this might impact on the generalisability of the results to a UK setting. Patients with poor renal function (creatinine clearance

< 30ml/minute) were excluded from the trials on the basis that they could not be randomised to zoledronic acid as the drug would be contraindicated for them. Therefore the effects of denosumab on patients with advanced cancer with bone metastases and poor renal function are unknown. However it has been estimated that less than 2% of patients with solid tumours have sufficiently poor renal function to avoid zoledronic acid.[208] The RCT for other solid tumours (excluding breast or prostate) pooled data from patients with a range of different types of solid tumour.

In addition the direct evidence from the trials comparing denosumab with zoledronic acid is only generalisable to those patients with advanced cancer and bone metastases for whom clinical guidance advocates the use of bisphosphonates. For breast cancer, this applies to all patients with advanced breast cancer and newly diagnosed bone metastases.[45] For prostate cancer, it applies to men with hormone-refractory prostate cancer with painful bone metastases for whom other treatments (including analgesics and palliative radiotherapy) have failed.[46] For lung cancer and other solid tumours there is no clear guidance on when bisphosphonates should be administered.[48] 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 analgesics.

*Network-meta-analysis*

There are several uncertainties associated with the network meta-analysis. Although caution was exercised when selecting trials for inclusion in the NMA, some differences inevitably exist between included studies in terms of populations and trial methodologies and this can lead to uncertainty in any meta-analysis with potential for further bias in an NMA. There were primary studies (other than those comparing denosumab) which did not report complete results, so some treatment effects used in the NMA (including levels of precision of the effects) were estimated and therefore subject to uncertainty despite the robust estimation methods employed. The small number of trials in each of the NMAs add to the uncertainty in the results, particularly as some of the individuals trials were small themselves and there were no instances (for any comparison between two treatments within an NMA) where there was sufficient comparable direct evidence to include more than one trial. This small amount of data resulted in wide ranges of parameter estimates at the extremes of the posterior distributions due to possible errors in simulation, despite convergent models. The estimates of treatment for the time-dependent outcomes were therefore presented with bootstrapped confidence intervals to address this consequence from the small amount of data, although in this context it resulted in narrower confidence intervals which should be interpreted accordingly. Further uncertainty may have resulted from the potential for different assumptions to be made when

specifying NMA models (e.g. in relation to baseline prior distributions) and this could be illustrated by differences between the NMA results in this assessment and the manufacturer's analysis. Although a different approach to the manufacturer was taken, many of the results from the manufacturer's indirect comparisons can be accurately replicated, which may mitigate some of the uncertainty associated with the NMA.

*SREs as a composite endpoint*

SREs are composite endpoints used in research studies and generally defined as including pathological fracture, requirement for radiation therapy to bone, surgery to bone, or spinal cord compression. These endpoints include both complications of bone metastases (pathological fracture and spinal cord compression) and therapeutic or preventative measures (radiotherapy and surgery). In the three denosumab RCTs the distribution of type of SRE was similar across treatment groups, for both time to first on-study SRE and risk of first-and-subsequent SREs. The vast majority of SREs consisted of pathological fracture or radiation to bone, with far fewer occurrences of spinal cord compression or surgery to bone. The three RCTs reported a statistically significant difference in favour of denosumab for time to first on-study SRE. [redacted] 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. This could potentially create the impression that the treatment is equally effective for each component of the composite endpoint when in fact this may not be supported by the evidence.

*Symptomatic versus non-symptomatic SREs*

The impact on patients of pathological fractures varies from unnoticeable, asymptomatic fractures to vertebral fractures associated with spinal cord compression that result in paraplegia. Patients in the denosumab RCTs underwent X-rays before treatment and at 12-weekly intervals during the study to detect the occurrence of pathological fractures or spinal cord compression. This skeletal survey frequency is unlikely to be the case in clinical practice. More frequent tests may have resulted in asymptomatic pathological fractures being detected that would have remained undetected in clinical practice. Also, in the RCTs once a SRE had been detected and classified as asymptomatic it could not later be reclassified as symptomatic – this could potentially lead to a rate of symptomatic SREs detected that was lower than that observed in clinical practice, on the basis that in clinical practice asymptomatic fractures would likely remain undetected until they had become symptomatic. Trinkaus and colleagues[37] compared observational SRE frequency in clinical practice with SRE

frequency in the intravenous bisphosphonate trials and reported a higher rate of SREs in the trial setting compared to clinical practice.

The manufacturer's submission stated that clinical expert opinion indicated that in clinical practice spinal cord compressions were symptomatic. For pathological fractures, vertebral fractures were predominantly asymptomatic whilst non-vertebral fractures were predominantly symptomatic based on their respective skeletal locations. In the denosumab RCTs, for time to first on-study SRE, and risk of first-and-subsequent SREs respectively, the percentage of fractures that were vertebral were [redacted] and [redacted] in the breast cancer trial, [redacted] and [redacted] in the prostate cancer trial and [redacted] and [redacted] in the other solid tumours trial.

*21 day window*

More than one SRE may occur in relation to a single event. For example an individual may suffer a pathological fracture, which is treated by radiotherapy or surgery (two SREs related to one event). Therefore in order to provide an estimate of the number of SRE events rather than just the overall number of SREs, in the denosumab and bisphosphonate trials a subsequent SRE was counted as a separate SRE only after a defined period (usually 21 days). 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.

*Overall survival*

In the three denosumab RCTs overall survival was reported as similar. However a post hoc analysis of the non-small cell lung cancer subgroup of the other solid tumours RCT by Henry and colleagues[30] reported a statistically significant difference in favour of denosumab (HR 0.79, 95% CI 0.65 to 0.95). A recent paper by Scagliotti and colleagues reported this difference as a median 9.5 months for denosumab and 8.1 months for zoledronic acid (HR 0.78, 95% CI 0.65 to 0.94).[209] Henry and colleagues[30] postulated that the difference in survival observed in this post hoc analysis might be due to differences in prognostic variables at study entry in a highly heterogeneous population or due to differences in specific antineoplastic treatments while on-study. The AG are of the opinion that this result should be interpreted with caution until further evidence is available.

*Appropriateness of analysing different tumour types together*

The denosumab RCT of other solid tumours (post hoc study 244) analysed a number of different primary tumour types together. The tumour types (%) were: non-small cell lung cancer (44.0%), [redacted]

[redacted]. Combining tumour types within a trial increases the risk of selection and performance bias. In addition, because of the small numbers of each tumour type, it is difficult to conclude if an intervention is more effective in one tumour type than another. However it would not be practical to conduct sufficiently powered trials on each tumour type and combining tumour types would be required at some stage.

*Bisphosphonates*

It was our intention to compare denosumab with zoledronic acid, disodium pamidronate, ibandronic acid and sodium clodronate. However only head-to-head evidence was available for denosumab compared with zoledronic acid. In breast cancer, pamidronate was suitable for inclusion in the network meta-analysis and indirect comparison with denosumab was possible. Due to lack of evidence the assessment of the effectiveness of denosumab compared with ibandronic acid and sodium clodronate was not possible. In addition it was not possible to compare the different routes of bisphosphonate treatments because of the inadequacy of data for indirect comparison. However, based on advice from clinical experts zoledronic acid is the most widely used bisphosphonate and should be used as the primary bisphosphonate comparator.

### *13.1.4 Other relevant factors*

*Place of denosumab in the care pathway*

There are various places at which denosumab could be considered in the care pathway. Current evidence only assesses denosumab compared with zoledronic acid as a first line treatment for the prevention of SREs. Denosumab could also be considered in patients who have had a previous SRE. In the denosumab trials individuals who had a previous SRE at baseline were at higher risk than those who did not have an SRE at baseline. Subgroups of patients with and without an SRE at baseline were reported. Denosumab significantly delayed the time to first SRE in those patients without a history of SRE for time to first on-study SRE and reduced the risk of first-and-subsequent SREs compared with zoledronic acid. 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.

Other places denosumab could be considered in the care pathway are, as a second line agent to those who continue to have SREs on current recommended treatment (bisphosphonates or best supportive care) or in patients who are contra-indicated to bisphosphonates. All patients in the pivotal denosumab trials were naive to bisphosphonates for bone metastases. Therefore no evidence was found for the use of denosumab in patients previously prescribed a bisphosphonate. Patients with severe renal

impairment were excluded from the pivotal trials. Therefore the effectiveness of denosumab in patients with advanced cancer and severe renal impairment is unknown.

*Potential for community-based treatment*

Denosumab is administered by monthly subcutaneous injection, while zoledronic acid is administered in hospital by intravenous infusion over at least 15 minutes every 3-4 weeks. Therefore patients receiving denosumab who were not otherwise required to attend hospital could potentially receive community-based treatment, which they (and their carers) might find more convenient in terms of, for example, having less distance to travel.

*Physiology of bone metastases between tumour types*

Bone metastases result in an imbalance of osteoclast and osteoblast activity. Traditionally it was thought that bone metastases could be osteolytic (also known as osteoclastic), osteoblastic or mixed. However current opinion is that a spectrum exists with no metastasis being purely osteolytic or osteoblastic. 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. Since denosumab inhibits osteoclasts, one might expect denosumab to be more effective in preventing complications associated with osteolytic lesions. However osteoclasts also affect osteoblastic function. A subgroup of the study comparing zoledronic acid and pamidronate in breast cancer found that patients with predominately lytic lesions responded better to zoledronic acid.[110] The pivotal denosumab studies did not report a subgroup of patients by lesion type.

*Bone markers*

Despite the clinical benefits of denosumab and bisphosphonates, only a proportion of SREs is prevented, and some patients may not experience a skeletal event despite the presence of metastatic bone disease. It has been suggested that bone markers could be used to stratify risk to individuals with bone metastases.[27,28] There are several different types of bone markers, including bone-specific alkaline phosphate (BSAP), osteocalcin and N-terminal type 1 procollagen peptides (PINP) for monitoring bone formation and urinary or serum collagen type 1 cross-linked C-telopeptide (CTX) and N-terminal propeptide of type 1 collagen (NTX) for monitoring bone resorption. The ASCO guidelines[34] currently do not recommend the use of bone markers in breast cancer outwith the trial setting.

*Ongoing studies*

Five ongoing studies of denosumab were reported by the manufacturer. Two studies are open label extensions of the Stopeck trial[31] and Fizazi trial.[29] One phase II study is currently evaluating

denosumab for prolonging bone metastasis-free survival in hormone refractory prostate cancer. There are also two phase two studies in progress, one investigating the use of denosumab for the treatment of hypercalcaemia and the other evaluating the effectiveness of denosumab in giant cell tumour of the bone.

## 13.2 Cost-effectiveness

### *13.2.1 Statement of principal findings*

AG within trial analyses suggest that for breast cancer patients denosumab results in a slightly lower average number of SREs compared to zoledronic acid, and that this will translate into a small average annual gain of perhaps 0.003 to 0.006 QALYs: roughly equivalent to one to two additional days in full health or two to three days at the SRE naïve quality of life. Without the PAS the additional cost of denosumab does not justify these relatively minor gains. With the PAS denosumab is estimated to be broadly cost neutral to slightly cost saving, and so cost effective compared to zoledronic acid.

Within trial analyses suggest that for prostate cancer patients denosumab results in a slightly lower average number of SREs compared to zoledronic acid. This translates into a slightly larger additional average annual gain of perhaps 0.008 to 0.016 QALYs. The reason for this difference for prostate cancer is the greater proportion of spinal cord compressions within the overall number of SREs. However, there is a suggestion that there may be slightly fewer zoledronic acid administration per annum than denosumab administrations. This triangulates with the higher proportion of zoledronic acid patients within the prostate cancer trial having doses withheld for creatine clearance. This aspect is not formally considered in either the manufacturer or the AG economic model.

Without the PAS the additional cost of denosumab still does not justify the relatively minor estimated gains. With the PAS, [redacted] denosumab is estimated as to increase annual costs by around £100 which translates into cost effectiveness estimates of between £6,545 per QALY and £15,272 per QALY. However, this AG within trial analysis does not distinguish between SRE naïve and SRE experienced patients.

For the cost utility modelling within breast cancer, the lifetime gains across all patients are estimated to be around 0.013 QALYs. This is again small, and does not justify the additional cost of £1,691 per patient compared to zoledronic acid. With the PAS [redacted] denosumab is estimated to dominate zoledronic acid. But for those contraindicated to bisphosphonates the cost effectiveness is poor: even with the PAS the cost effectiveness is £158,844 per QALY. Applying the SRE naïve and SRE experienced subgroup specific clinical effectiveness has little impact upon the results, as these estimates are reasonably close to the pooled all patient estimates.

For the cost utility modelling within prostate cancer, across all patients the gain from denosumab over zoledronic acid is around 0.020 QALY while compared to BSC it is 0.030 QALYs, at net costs without the PAS of £941 and £3,880 respectively. Without the PAS, compared to zoledronic acid this results in a cost effectiveness of £46,976 per QALY. Cost effectiveness is estimated to be slightly better among the SRE naïve at £35,732 per QALY, but the quid pro quo is a worse cost effectiveness among the SRE experienced of £167,503 per QALY. This may arise in large part due to the estimated step change in HRQoL arising from a patient's first SRE.

With the PAS, denosumab is estimated to be cost saving compared to zoledronic acid and so dominate it. For those contraindicated to bisphosphonates, denosumab is not estimated to be cost effective compared to BSC. Applying the SRE naïve and SRE experienced subgroup specific clinical effectiveness has a reasonably large impact upon the results. But the PAS [redacted] resulting in denosumab being estimated to remain dominant over zoledronic acid.

Within the cost utility modelling of other solid tumours including lung, the gains from denosumab over zoledronic acid are estimated to be less than 0.01 QALYs. Without the PAS denosumab is not cost effective, but with it the small additional overall costs of around £100 result in cost effectiveness estimates of between £11,800 per QALY and £13,900 per QALY. The impact of applying the SRE subgroup specific estimates within this group is quite large. While it improves the cost effectiveness estimates of denosumab compared to BSC for SRE naïve patients, even with the PAS it is not sufficient to render it cost effective due to the SRE experienced relative risk for SREs being [redacted]

For lung cancer, possibly due to the short life expectancy the patient gains from denosumab over zoledronic acid among SRE experienced patients are estimated to be small: 0.003 QALYs. Even with the PAS, the additional cost of £118 results in a cost effectiveness of £42,698 per QALY.

If the price of zoledronic acid falls by only a reasonably small amount at patent expiry, the cost effectiveness of denosumab compared to it will change dramatically due to the very small estimate for patient gains.

### *13.2.2 Strengths and limitations of the assessment*

The assessment group analysis is in part framed by the manufacturer analysis in terms of outlook and approach. The cost utility modelling relies upon it for the greater part of its input, due to a paucity of other data sources for elements such as quality of life values. But the broad conclusions of the

assessment appear relatively insensitive to the approach adopted, as shown by the much simpler within trial analyses.

### *13.2.3 Uncertainties*

A concern within the modelling is BSC being assumed to have a zero incidence of the modelled SAEs. When the benefits from active treatments upon SREs are muted, there is the possibility that SAEs come to the fore and require a more detailed consideration. Sensitivity analyses that completely exclude SAEs from the analysis do improve the cost effectiveness of denosumab compared to BSC, but this in itself is not sufficient to render denosumab cost effective compared to BSC when this is the appropriate comparator.

There remains some uncertainty around the reasonableness of the utility estimates applied. In particular the step change estimated between SRE naïve patients and SRE experienced patients provides much of the gain anticipated from SRE naïve patients avoiding their first SRE. Whether this estimate is picking up the impact other variables such as progression which are not considered in the utility estimates is currently an open question.

A key uncertainty is the rate of paralysis associated with spinal cord compression and the duration of quality of life impact from spinal cord compression. Extending the average quality of life decrement measured in the five months subsequent to the compression through to death improves the estimated cost effectiveness, particularly among SRE naïve prostate cancer patients. While not in itself sufficient to render denosumab cost effective against BSC, extending the impacts of spinal cord compression does improve the cost effectiveness. There are also some concerns that the ongoing costs of spinal cord compression may have been underestimated.

Probabilistic modelling suggests that within the usual range of cost effectiveness thresholds there is relatively little uncertainty around the cost effectiveness acceptability frontier. The central estimates are also in line with those of the deterministic analyses.

# 14 CONCLUSIONS

## 14.1 Implications for service provision

Denosumab is effective in delaying the time to first SRE and reducing the risk of developing first-and-subsequent SREs in patients with bone metastases from breast cancer and prostate cancer. For non-small cell lung cancer (NSCLC), for time to first SRE the direction of effect favoured denosumab without being statistically significant, [redacted] For other solid tumours (excluding breast, prostate and NSCLC), denosumab was effective in delaying the time to first SRE, [redacted] The distribution of type of SRE was similar across treatment groups, with the vast majority consisting of pathological fracture or radiation to the bone, [redacted], while there were few occurrences of spinal cord compression or surgery to bone.

Denosumab was also shown to be effective in delaying the time to development of moderate or severe pain (for the subgroup of patients with no or mild pain at baseline) for patients with breast cancer and those with other solid tumours (including NSCLC) but the difference was smaller for prostate cancer. The median time to worsening pain was generally similar for the treatment groups in the three studies. In terms of quality of life, across all three RCTs FACT scores remained similar between the groups [redacted]. Overall survival was reported to be similar in the studies apart from the post hoc analysis of NSCLC where a statistically significant difference was reported in favour of denosumab.

In both the Assessment Group's network meta-analysis, there was a statistically significant difference in favour of denosumab for both time to first SRE and risk of first-and subsequent SRE, [redacted]. However the results of the network meta-analyses are subject to considerable uncertainty and should be interpreted with caution.

The effectiveness of denosumab compared with zoledronic acid and best supportive care in delaying time to first SRE and reducing the risk of first and subsequent SREs has been demonstrated. These results have mostly reached statistical significance and met the minimally clinically significant change described by clinical experts (delay of more than 3 months or HR reduction of more than 20%). However the importance of the composite SRE outcome, and spectrum of corresponding possible health states, to an individual patient is not clear. Evidence for the effectiveness of denosumab compared with zoledronic acid in reducing pain and improving relative quality of life is less evident.

The manufacturer model, the assessment group within trials analyses and the assessment group cost utility model all estimate denosumab to result in patient benefits from reduced SREs compared to denosumab, and larger benefits compared to best supportive care. But the estimates of the numbers of SREs avoided per patient are small, when compared to zoledronic acid typically less than 0.3 SREs over the patient lifetime and often a lot less than this. Spinal cord compression is relatively rare. The QALY gains from the number of SREs avoided compared to zoledronic acid are small, typically less than 0.02 QALYs over the patient lifetime and again often quite a lot less than this.

[redacted]

Given this and the small QALY gains, denosumab is in the main estimated to dominate or be cost effective compared to zoledronic acid. But zoledronic acid comes off patent quite soon. [redacted] price reduction of [redacted] for zoledronic acid is required to result in the additional net costs from denosumab rendering it not cost effective at current thresholds. 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.

### 14.2 Suggested research priorities

Further research would be helpful in the following areas:

- The effectiveness of denosumab compared with zoledronic acid in delaying time to first SRE and reducing the risk of first-and-subsequent SREs in patients with hormone-refractory prostate cancer and painful bone metastases for whom other treatments, including analgesics and palliative radiotherapy, have failed.
- Whether there is an identifiable subgroup of patients at higher risk of spinal cord compression for whom denosumab might result in larger QALY gains.
- The safety and efficacy of denosumab in patients with severe renal impairment and advanced cancer (breast, prostate, non-small cell lung and other solid tumours).
- The safety and efficacy of denosumab in patients with advanced cancer who have previously been exposed to a bisphosphonate.
- The role of bone markers (including BSAP, PINP, CTX and NTX) to identify subgroups of patients with advanced cancer and bone metastases who may be likely to benefit from bone targeting therapies.
- The effectiveness of denosumab compared with zoledronic acid for overall survival in patients with non-small cell lung cancer and bone metastases.

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