NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Multiple Technology Appraisal (MTA)

Denosumab for the treatment of bone metastases from solid tumours

Manufacturer/sponsor submission of evidence

Amgen Limited

Confidential information is highlighted and underlined; mark-up of commercial and academic in confidence will be finalised in the final draft dossier

Executive summary

Introduction

Bone metastases are estimated to affect over 150,000 patients with solid tumours in England and Wales and can result in incapacitating clinical sequelae including pathological fractures, radiation to bone, spinal cord compression, or surgery to bone; collectively defined as skeletal-related events (SREs). These SREs can dramatically erode quality of life and the pain associated with bone metastases and SREs is significant, debilitating and difficult to treat. The prevention or delay of SREs can therefore provide meaningful benefits to patients.

Denosumab (XGEVA®) is an innovative new biological therapeutic for the prevention of SREs in cancer patients with bone metastases, with a unique mechanism of action and convenient, NHS resource-releasing mode of administration. Through its precise, targeted mechanism of action, denosumab offers a significant scientific advance, with an associated medical step-change in the treatment of patients with bone metastases from solid tumours. Denosumab has demonstrated a superior, statistically significant, clinically meaningful, consistent and robust treatment effect for the reduction in the occurrence of SREs compared with zoledronic acid in breast, prostate and other solid tumours, across three Phase III randomised controlled trials (RCTs). This was accompanied by a delay in the time to moderate or severe pain for denosumab compared to zoledronic acid. These Phase III studies represent the largest and most robust evidence package constructed to-date in SRE prevention in patients with bone metastases. Further, unlike bisphosphonates, denosumab can be used in patients regardless of renal function or concomitant use of nephrotoxic drugs, providing a safe and effective treatment for patients with renal impairment. Denosumab is administered as a simple subcutaneous injection, avoiding the burden of intravenous access and infusion and the potential complications of acute phase reactions associated with bisphosphonates. Denosumab also offers the opportunity for the treatment of patients with bone metastases out of the hospital setting (e.g. primary care or community) reducing the burden for both patients and the NHS.

The cost-effectiveness analyses presented in this submission are based on the proposed list-price of denosumab. Amgen have proposed a Patient Access Scheme (PAS) to the Department of Health which is undergoing consideration by the Patient Access Scheme Liaison Unit. When the PAS is incorporated into the cost-effectiveness analyses, denosumab represents a cost-effective option for the prevention of SREs in adults with bone metastases from solid tumours.

In the UK, based on NICE clinical guidelines and resulting bisphosphonate treatment patterns, when incorporating the PAS, denosumab represents a cost-effective treatment option for the prevention of SREs in the following patient groups:

- Breast cancer patients with bone metastases
- Prostate cancer patients with painful bone metastases who have experienced a prior SRE
- Other solid tumour patients with painful bone metastases who have experienced a prior SRE.

Description of the Technology

United Kingdom (UK) approved name: Denosumab

Brand name: XGEVA®

Marketing status: Denosumab does not currently have a UK marketing authorisation for the indication under consideration in this appraisal. An application for marketing authorisation (centralised process) was made by Amgen to the European Medicines Agency (EMA) in June 2010. The CHMP issued a positive opinion for the marketing authorisation of XGEVA® (denosumab), for the prevention of skeletal-related events in adults with bone metastases from solid tumours on 19th May 2011. Additionally, the CHMP recommended a one-year market exclusivity extension for XGEVA® in the EU, because it would bring a significant clinical benefit in comparison with existing therapies for this indication. If approved by the European Commission, marketing authorisation for XGEVA® in all European Union (EU) Member States is expected in August 2011.

Principal pharmacological action: Denosumab is a fully human monoclonal immunoglobulin (Ig)G2 antibody. It is an innovative new therapeutic for cancer patients with bone metastases and has a precise, targeted and unique mechanism of action.

The formulation, strength, pack size, maximum quantity, anticipated frequency of any repeat courses of treatment and acquisition cost: Denosumab for the prevention of SREs is formulated as a solution for injection (containing 120 mg of denosumab in 1.7 ml of solution) in a vial. Denosumab is administered as a single subcutaneous injection into the thigh, abdomen or upper arm. For the prevention of skeletal-related events the injection is repeated once every four weeks. The acquisition cost is £309.86 per 120 mg vial, which is equivalent to £4,028.18 for one full year of treatment (thirteen doses). Denosumab is suitable for administration in primary, community or secondary care settings.

Indication: The indication being sought in the UK 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'.

Restrictions: It is not anticipated that the marketing authorisation will be subject to any special conditions or restrictions.

Recommended course of treatment: Continuous treatment – administered as a subcutaneous injection once every four weeks for the prevention of SREs.

Selection of comparators for this technology appraisal

Selection of bisphosphonate comparators for each tumour type is based on relative effectiveness, NICE clinical guidelines and resulting bisphosphonate treatment patterns. Zoledronic acid is the primary bisphosphonate comparator across all tumours types, since it is the most commonly used bisphosphonate within the UK and is considered to be the standard of care. Zoledronic acid is the most effective bisphosphonate and is the only bisphosphonate with demonstrated efficacy based on randomised controlled clinical trials across the entire range of solid tumours (breast, prostate and other solid tumours), and specifically the only

bisphosphonate demonstrating efficacy in patients with prostate cancer and other solid tumours. Bisphosphonates identified as potential comparators, but with a tumour specific patient treatment share of ≤5%, have been excluded since they may be plausibly deemed to not represent UK clinical practice for this indication.

Breast cancer: NICE clinical guidelines for breast cancer (CG81) recommend that bisphosphonates should be considered for use in advanced breast cancer patients with bone metastases. The adoption of these guidelines in clinical practice is reflected by high bisphosphonate treatment rates (87% of patients with bone metastasis). Zoledronic acid is the primary comparator in breast cancer since it is the most effective and represents the bisphosphonate most commonly used (50% of treated patients). In addition, based on UK treatment patterns, ibandronic acid (31% of treated patients) and disodium pamidronate (18% of treated patients) are relevant supplementary comparators.

Prostate cancer: NICE clinical guidelines (CG58 and CG75) recommend against the use of bisphosphonates in prostate cancer patients with bone metastases who are free of pain and have not experienced a prior SRE, but do recommend the use of bisphosphonates for pain management in patients with painful bone metastases who have experienced a prior SRE. NICE clinical guidelines (CG58), for prostate cancer, recommend that bisphosphonates should be considered for pain relief when other treatments, including analgesics and palliative radiotherapy (itself a frequently observed SRE) have failed. In addition, the NICE clinical guidelines (CG75) in the diagnosis and management of adults at risk of and with metastatic spinal cord compression (also a defined SRE) recommend the use of bisphosphonates to reduce pain in patients with prostate cancer, if conventional analgesia fails. This therefore reinforces the CG58 recommendation that bisphosphonates are restricted in patients with prostate cancer to those with painful bone metastases who have experienced a prior SRE. Bisphosphonates are used in approximately half (49%) of prostate cancer patients with bone metastases, reflecting NICE recommendations for their restricted use.

Zoledronic acid is the primary comparator for this restricted patient population since it is the only bisphosphonate with demonstrated efficacy in SRE prevention in prostate cancer and represents the bisphosphonate most commonly used (92% of treated patients). In patients with prostate cancer who would not be treated with bisphosphonates in the UK, as they are free of pain or have pain but have not experienced a prior SRE, best supportive care (defined as no active treatment) has been identified as the primary comparator.

Other solid tumours: There are no NICE clinical guidelines recommending the use of bisphosphonates in other solid tumours (excluding breast and prostate cancer). There are recommendations for the management of painful bone metastases in lung cancer and also in metastatic spinal cord compression. However there is an absence of recommendations for the management of patients who fail recommended therapy (radiotherapy) and continue to experience painful bone metastases in other solid tumours.

NICE clinical guidelines in lung cancer (CG121) recommend that single-fraction radiotherapy should be administered for patients with bone metastasis requiring palliation and for whom

standard analgesic treatments are inadequate. Further, NICE clinical guideline (CG75 – diagnosis and management of adults at risk of and with metastatic spinal cord compression) states that bisphosphonates should not be used to treat spinal pain in patients with vertebral involvement from other solid tumours (if conventional analgesia fails) or with the intention of preventing metastatic spinal cord compression except as part of a randomised controlled trial. Therefore NICE clinical guidelines make no recommendations on the treatment of those patients with lung or other solid tumours that have failed both conventional analgesics and palliative treatment with radiotherapy (a common defined SRE) and continue to experience painful bone metastases.

Bisphosphonates are used in over one-third (37%) of patients with other solid tumours (excluding breast and prostate) with bone metastases in the UK. Based on expert clinical opinion, it is understood that bisphosphonates are used selectively for the treatment of patients with other solid tumours in the same way that they are used in prostate cancer (patients with painful bone metastases who have experienced a prior SRE).

Zoledronic acid has been deemed the primary comparator for this restricted patient population since it represents the bisphosphonate most commonly used (80% of treated patients) and it is the only bisphosphonate with demonstrated efficacy across a broad range of other solid tumours. Disodium pamidronate is considered a supplementary comparator in patients with other solid tumours, since it is used in 20% of bisphosphonate-treated patients, although there is no clinical evidence reporting efficacy in SRE prevention to support its use. In patients with other solid tumours who would not be treated with bisphosphonates in the UK as they are free of pain or have pain but have not experienced a prior SRE, best supportive care (defined as no active treatment) has been identified as the primary comparator. A summary of the comparators is provided in Table 1.

Table 1. Primary and supplementary comparators for denosumab by primary tumour and population

Comparator Selection	Primary Tumour				
	Breast cancer	**Prostate cancer**		**Other solid tumours (excluding breast and prostate cancer)**	
Population	All patients	No pain or pain with no prior SRE	Pain and prior SRE	No pain or pain with no prior SRE	Pain and prior SRE
Primary comparator	Zoledronic acid	BSC	Zoledronic acid	BSC	Zoledronic acid
Supplementary comparators	Disodium pamidronate and ibandronic acid	None	None	None	Disodium pamidronate

BSC, best supportive care; SRE, skeletal related event

Key clinical evidence

A systematic review was used to identify relevant randomised controlled trials (RCTs). The key clinical evidence for denosumab comes from three Phase III, head-to-head, comparator RCTs, conducted in a broad range of advanced solid tumours, which were identically designed to allow an integrated analysis of both efficacy and safety; Study 136 in breast cancer, Study 103 in castrate-resistant prostate cancer and Study 244 in other solid tumours (excluding breast and prostate) or multiple myeloma (MM).

At the request of the Institute, and in order to align with the marketing authorisation recommended by the CHMP, efficacy data presented within this submission comes from post-hoc analyses excluding MM; both for Study 244 (other solid tumours) and for the integrated analysis of Studies 136, 103 and 244 (integrated analysis across all solid tumours). Although the analysis was not pre-specified, other solid tumours and multiple myeloma were stratification factors in Study 244. In addition there is a strong clinical rationale to perform an analysis of patients with other solid tumours only.

Each of the Phase III studies evaluated denosumab versus zoledronic acid (the standard of care). Zoledronic acid is the only bisphosphonate with demonstrated efficacy across breast, prostate and other solid tumours and has been identified as the primary comparator across all solid tumour types for this appraisal. The primary outcome measure was the clinically relevant end point of time to first composite SRE (defined as pathological fracture, radiation to bone, surgery to bone or spinal cord compression). All studies were powered to detect both non-inferiority and superiority.

Results from these three large and adequately powered (for superiority) RCTs forms a robust and comprehensive body of evidence for this appraisal, in which a total of 5,554 solid tumour patients were evaluated for efficacy in 2,046 patients with breast cancer, 1,901 patients with prostate cancer and 1,597 patients with other solid tumours (excluding MM). This represents the largest and most robust evidence package constructed to-date in SRE prevention in patients with bone metastases.

There were no head-to-head RCTs comparing denosumab with other treatments for patients with bone metastases from solid tumours, since from a regulatory perspective, direct, head-to-head evaluation against the most effective bisphosphonate was considered sufficient to demonstrate efficacy in patients with solid tumours. However, in order to address the decision problem set out in this appraisal, a network meta-analysis (NMA) was used to assess the comparative efficacy of denosumab against all identified relevant comparators.

The NMA involved a total of 17 RCTs (11 in breast cancer, two in prostate cancer and four in other solid tumours), evaluating up to four SRE endpoints. There were significant limitations to the evidence available to inform this NMA: while there was a large data package evaluating denosumab versus zoledronic acid, there was only a small number of RCTs to support each of the other comparators within the NMA, with much lower patient numbers. A key limitation of NMA is that estimates based on them can be no more precise than the least precise data of the network chain. In this case there was a large body of evidence comparing denosumab with zoledronic acid (2,046, 1,901 and 1,597 patients with breast cancer, prostate cancer and other

solid tumours respectively), but only a small body of evidence evaluating disodium pamidronate (1,005 patients with breast cancer only) and ibandronic acid (462 patients with breast cancer only). Therefore, the NMA suffered from lack of information on disodium pamidronate and ibandronic acid, and for this reason it provided little useful information on the relative efficacy of denosumab versus these two treatments. There were also differences in baseline characteristics of the patient populations and dates when trials were conducted. These smaller sized comparator trials may impact the conclusions that can be drawn from this NMA. Simple adjusted indirect comparisons are generally underpowered; four times as many equally sized studies are needed to achieve the same power as direct comparisons and frequently lead to indeterminate results with wide confidence intervals. There was also incomplete SRE endpoint data for some comparators. Due to the limited number of trials available, limited data reported within trials and potential departures from the assumptions of similarity, the results of the NMA should be viewed cautiously and considered inconclusive.

The Phase III studies compared denosumab directly with zoledronic acid, which is the primary bisphosphonate comparator across all tumours types for this technology appraisal. This represents the largest and most robust evidence package constructed to-date in SRE prevention in patients with bone metastases. Therefore, more weight should be given to the relevance of this evidence package than the NMA (with its inherent limitations) when evaluating the clinical and cost-effectiveness of denosumab.

1. Overview of direct head-to-head clinical evidence for denosumab versus zoledronic acid

Results from the Phase III denosumab studies 136, 103 and 244, evaluating efficacy in patients with advanced breast cancer, prostate cancer and other solid tumours, demonstrated a superior, statistically significant, clinically meaningful, consistent and robust treatment effect of denosumab across all solid tumour types for the reduction in the occurrence of SREs compared to zoledronic acid.

SRE outcomes: Denosumab demonstrated superior efficacy versus zoledronic acid, significantly reducing the risk of first on-study SRE by 18% in breast cancer (p = 0.01, adjusted p value) and prostate cancer (p = 0.008, adjusted p value), and by 19% in other solid tumours (p = 0.034, adjusted p value, post hoc analysis). There was a significant delay in median time to first on-study SRE compared with zoledronic acid in patients with breast cancer (not reached versus 26.4 months), prostate cancer (20.7 versus 17.1 months, 3.6 month delay) and other solid tumours ([redacted] versus [redacted] months, [redacted] month delay).

Denosumab significantly reduced the risk of developing multiple SREs (first-and-subsequent on-study SREs) compared with zoledronic acid, by 23% in breast cancer (p = 0.001), 18% in prostate cancer (p = 0.008) and 15% in other solid tumours (p = 0.048, post hoc analysis). Furthermore this analysis, which assessed the total burden of SREs, demonstrated a clinically relevant difference in the total number of SREs; denosumab decreased the total number of SREs compared to zoledronic acid by approximately [redacted]% ([redacted] versus [redacted] events) in breast

cancer, by [redacted]% ([redacted] versus [redacted] events) in prostate cancer and by [redacted]% ([redacted] versus [redacted] events) in other solid tumours.

The efficacy of denosumab was sustained over time, in each of the Phase III studies and in the integrated analysis across all solid tumours. The distributions of SRE type for first and first-and-subsequent on-study SREs were similar for denosumab and zoledronic acid treatment groups for individual studies and across all studies, with pathological fractures and radiation to the bone being the most frequently reported. In the integrated analysis across all solid tumours, of first on-study SREs, [redacted]% versus [redacted]% of patients had pathological fractures and [redacted]% versus [redacted]% of patients had radiation to the bone respectively. No inconsistency in efficacy was observed across the individual SRE components of the composite SRE endpoint; in the integrated analysis across all solid tumours for time to first on-study SRE, the magnitude of effect for denosumab was consistent for each SRE component. Furthermore, homogeneity testing showed no evidence of inconsistent effect across the four SRE components.

Patient reported outcomes: Denosumab delayed the time to development of moderate or severe pain compared with zoledronic acid (in patients with no or mild pain at baseline) in breast cancer (median time; [redacted] versus [redacted] months, p [redacted] in prostate cancer (5.8 versus 4.9 months, p = 0.1416) and in other solid tumours ([redacted] versus [redacted] months, p [redacted]), and in the integrated analysis across all solid tumours ([redacted] versus [redacted] months, p [redacted]). Additionally, denosumab decreased the proportion of patients who progressed to moderate or severe pain in breast cancer (a relative decrease of [redacted]% over 73 weeks), prostate cancer (a relative decrease of [redacted]% over 73 weeks), other solid tumours (a relative decrease of [redacted]% over 45 weeks) and in the integrated analysis across all solid tumours (a relative decrease of [redacted]% over 41 weeks). In each of the Phase III denosumab studies and the integrated analysis across all solid tumours, fewer patients administered denosumab progressed from low analgesic use to strong opioids when compared to those taking zoledronic acid; [redacted]% over 73 weeks in breast cancer, [redacted]% over 73 weeks in prostate cancer, [redacted]% over 45 weeks in other solid tumours and [redacted]% over 41 weeks in the Integrated analysis across all solid tumours,

Subgroup analysis by prior SRE history: Subgroup analyses in each Phase III study showed that the relative treatment effect for time to first and time to first-and-subsequent on-study SRE was consistent in patients regardless of prior SRE history. The results of the covariate analysis showed that prior SRE history was associated with a greater absolute risk of both first, and first-and-subsequent, on-study SREs in each Phase III study; results showed that patients with a prior SRE history had a [redacted]%, [redacted]% and [redacted]% increased risk of first on study SRE compared to those without a prior SRE history, in patients with breast cancer, prostate cancer and other solid tumours respectively.

Overall survival and disease progression were similar for denosumab and zoledronic acid both within individual studies and in the integrated solid tumour analyses.

Safety: Safety data, from the three Phase III denosumab RCTs, was based on the 5,677 randomised patients who received ≥ 1 dose of active investigational product, and therefore

included patients with multiple myeloma. These data showed that denosumab was well tolerated and had a similar overall incidence of adverse events and serious adverse events compared to zoledronic acid. Despite the dosing of zoledronic acid in accordance with the approved prescribing information, renal toxicity was still evident in the zoledronic acid group. Consistent with its greater antiresorptive effect a higher incidence of hypocalcaemia was observed with denosumab compared with zoledronic acid; these events were mainly non-serious, transient, and either resolved spontaneously or with calcium supplementation. Osteonecrosis of the jaw **(**ONJ) was observed infrequently with denosumab and zoledronic acid, with no significant difference between treatment groups (1.8% and 1.3%, respectively, p = 0.1343). The clinical characteristics of these ONJ cases were similar in each group, with resolution rates higher in the denosumab group ([redacted]%) compared with the zoledronic acid group ([redacted]%). There was no evidence of an increased risk for clinically relevant adverse outcomes, such as reduction in overall survival or progression of the underlying cancer, new malignancies, infections (including serious skin infections), eczema, cataracts, or cardiovascular events for denosumab compared with zoledronic acid. In summary, results from this comprehensive safety evaluation demonstrate that denosumab administration was well tolerated and had an acceptable safety profile.

2. Overview of indirect clinical evidence for denosumab versus additional comparators

Below is a summary of relative efficacy of denosumab versus each of the identified additional comparators. This is presented by tumour type and is based on available clinical evidence from the primary NMA. Due to the limited number of trials available, limited data reported within trials and potential departures from the assumptions of similarity, the results of the NMA should be viewed cautiously and considered inconclusive.

Breast cancer

Denosumab versus ibandronic acid and disodium pamidronate (supplementary comparators): An NMA was conducted to evaluate the efficacy of denosumab compared with ibandronic acid and disodium pamidronate. In addition to the head-to-head denosumab versus zoledronic acid study in 2,046 patients (Study 136), eight small RCTs were available for use within the primary NMA of all bisphosphonates, with available evidence for time to first and time to first-and-subsequent SRE. For the supplementary comparator disodium pamidronate, there were three studies – one versus zoledronic acid and two versus placebo (treating 254, 371 and 380 patients). For the supplementary comparator ibandronic acid there were two were placebo-controlled studies (treating 150 and 312 patients). The results of the NMA showed that [redacted]

Prostate cancer

Denosumab versus best supportive care (no active treatment): An indirect comparison was used to compare the efficacy of denosumab with best supportive care (no active treatment) in patients with prostate cancer. In addition to the head-to-head denosumab versus zoledronic acid study in 1901 patients (Study 103), one small placebo controlled RCT versus zoledronic acid was available (422 patients excluding trial arms with off-license dosing). The results of the NMA showed that [redacted]

Other solid tumours

Denosumab versus best supportive care (no active treatment): An indirect comparison was used to compare the efficacy of denosumab with best supportive care (no active treatment) in other solid tumours (excluding breast and prostate). In addition to the head-to-head denosumab versus zoledronic acid study in 1597 patients (Study 244), one small placebo controlled RCT versus zoledronic acid was available (507 patients). The results of the NMA showed that [redacted]

Summary of clinical evidence

In summary, there is robust RCT evidence to demonstrate a superior, statistically significant, clinically meaningful treatment effect of denosumab compared with the primary bisphosphonate comparator zoledronic acid, for the prevention of SREs in patients with breast cancer, prostate cancer and other solid tumours (post hoc analysis). In prostate and other solid tumours, where patients with painful bone metastases who have experienced a prior SRE are deemed the relevant patient population, subgroup analyses by SRE history have demonstrated a consistent treatment effect for denosumab versus the primary bisphosphonate comparator zoledronic acid. The absolute risk of SREs is higher in patients who have experienced a prior SRE. Moreover, in patients with a prior SRE history the proportion of patients with pain at baseline was high (80% and 86%) in prostate and other solid tumours respectively. Additionally, 75% and 72% of patients with a prior SRE history had received radiotherapy to the bone prior to entry into the studies respectively. Therefore, the patients in the RCTs appropriately represent those patients with prostate cancer and other solid tumours where denosumab will be used in clinical practice in the UK. That is patients with painful bone metastases who have experienced a prior SRE.

Cost-effectiveness

Type of economic evaluation and justification for the approach used: A cost-utility analysis was undertaken in accordance with the NICE reference case. A lifetime analysis was performed using a Markov model (cycle length = 28 days; half-cycle correction used). Costs and outcomes were discounted at 3.5% per annum. The SRE risk and event rates were derived from the Phase III studies for each tumour type (breast, prostate and other solid tumours). Data from the zoledronic acid arm of each Phase III study was used to estimate the baseline absolute risk of SREs. Treatment effects were estimated using the NMA. Utility weights were derived from the Phase III studies which included the administration of the EQ-5D instrument every four weeks during the studies. Drug therapy costs were taken from the British National Formulary. Bisphosphonate and denosumab administration costs were derived from a structured questionnaire conducted among appropriate UK healthcare professionals and a subsequent micro-costing analysis. SREs costs were derived from a prospective observational study in the UK and subsequent cost-estimation using NHS reference costs and Personal Social Services Research Unit. Monitoring and adverse events costs were based on NHS reference costs.

Pivotal assumptions underlying the economic model/analysis

Structural assumptions: The absolute risk of an SRE varies over time for the first SRE. The risk of recurrent SREs is constant over time; the distribution of the SRE types is kept constant over the time horizon with different SRE type distributions based on SRE history; mortality from cancer and non-cancer causes is assumed to be mutually exclusive; no AEs can be experienced while off treatment; none of the treatments have an effect on cancer disease progression or overall survival. Cancer disease progression was not modelled and survival was based on life tables (non-cancer death) and pooled data from zoledronic acid and denosumab was used for each tumour type: Study 136 (Breast), Study 103 (Prostate) and Study 244 (Other solid tumours) cancer mortality.

Treatment effect assumptions: The treatment effects are fixed over the time horizon and patients derive a constant relative reduction in their risk of SREs as long as they are on treatment. Upon treatment discontinuation patients are assumed to derive no treatment benefit (that is, a placebo treatment effect is used); the treatment effect of each treatment is considered by tumour type (as indicated in the NMA).

Comparator data gaps assumptions: In the absence of data on the treatment effect and on the frequency of AEs with disodium pamidronate in other solid tumours, efficacy data in breast cancer were used as the basis of assumptions. That is in the absence of efficacy evidence in other solid tumours, a treatment effect equivalent to that observed in breast cancer was bestowed on the unproven disodium pamidronate. The same frequency of AEs was used for disodium pamidronate in other solid tumours as observed in breast cancer; it was assumed that data on AEs for disodium pamidronate and ibandronic acid were directly comparable to AE data for zoledronic acid and denosumab based on the Phase III studies. The assumption was that these patient populations were comparable and that the same AE rates would be observed for each treatment if the patients from one trial had been switched with the patients from another trial; it was assumed that the study discontinuation rates for disodium pamidronate and ibandronic acid were directly comparable to the treatment discontinuation rates for zoledronic acid and denosumab.

Cost-effectiveness results

The cost-effectiveness analyses presented here are based on the list price of denosumab. Amgen have proposed a Patient Access Scheme (PAS) to the Department of Health which is undergoing consideration by the Patient Access Scheme Liaison Unit. When the PAS is incorporated into the cost-effectiveness analyses, denosumab represents a highly cost-effective option (dominates all comparators) for the prevention of SREs in all adults with bone metastases from breast cancer and in adults with painful bone metastases from prostate cancer or other solid tumours that have experienced a prior SRE.

Base-case results (incorporating the PAS):

Table 2. Population: Breast cancer patients with bone metastases

Treatment	Costs (£)	QALYs	Denosumab versus comparator		
			∆Costs (£)	∆QALYs	ICER (∆Cost/∆QALY)
Denosumab	[redacted]	1.912	-	-	-
Primary comparator					
Zoledronic acid	[redacted]	1.904	-483	0.007	Denosumab Dominant
Supplementary comparators					
Disodium pamidronate	[redacted]	1.898	-3,453	0.013	Denosumab Dominant
Ibandronic acid	[redacted]	1.907	-1,895	0.005	Denosumab Dominant

Table 3. Population: Prostate cancer patients with painful bone metastases who have experienced a prior SRE

Treatment	Costs (£)	QALYs	Denosumab versus comparator		
			ΔCosts (£)	ΔQALYs	ICER (ΔCost/ΔQALY)
Denosumab	[redacted]	1.089	-	-	-
Primary comparator					
Zoledronic acid	[redacted]	1.083	-281	0.006	Denosumab Dominant

Table 4. Population: Other solid tumours patients with painful bone metastases who have experienced a prior SRE

Treatment	Costs (£)	QALYs	Denosumab versus comparator		
			ΔCosts (£)	ΔQALYs	ICER (ΔCost/ΔQALY)
Denosumab	[redacted]	0.765	-	-	-
Primary comparatorX					
Zoledronic acid	[redacted]	0.761	-43	0.004	Denosumab Dominant
Supplementary comparator					
Disodium pamidronate	[redacted]	0.759	-2,918	0.006	Denosumab Dominant

Base-case results (not incorporating the PAS):

Table 5. Population: Breast cancer patients with bone metastases

Treatment	Costs (£)	QALYs	Denosumab versus comparator		
			ΔCosts (£)	ΔQALYs	ICER (ΔCost/ΔQALY)
Denosumab	[redacted]	1.912	-	-	-
Primary comparator					
Zoledronic acid	[redacted]	1.904	1,484	0.007	£203,387
Supplementary comparators					
Disodium pamidronate	[redacted]	1.898	-1,486	0.013	Denosumab Dominant
Ibandronic acid	[redacted]	1.907	72	0.005	£13,835

Table 6. Population: Prostate cancer patients with painful bone metastases who have experienced a prior SRE

Treatment	Costs (£)	QALYs	Denosumab versus comparator		
			ΔCosts (£)	ΔQALYs	ICER (ΔCost/ΔQALY)
Denosumab	[redacted]	1.089	-	-	-
Primary comparator					
Zoledronic acid	[redacted]	1.083	922	0.006	£157,276

Table 7. Population: Other solid tumours patients with painful bone metastases who have experienced a prior SRE

Treatment	Costs (£)	QALYs	Denosumab versus comparator		
			ΔCosts (£)	ΔQALYs	ICER (ΔCost/ΔQALY)
Denosumab	[redacted]	0.765	-	-	-
Primary comparator					
Zoledronic acid	[redacted]	0.761	757	0.004	£205,580
Supplementary comparator					
Disodium pamidronate	[redacted]	0.759	-2,118	0.006	Denosumab dominant

Conclusion

Denosumab (XGEVA®) is an innovative new biological therapeutic for the prevention of SREs in cancer patients with bone metastases, with a unique mechanism of action and convenient, NHS resource releasing mode of administration. Denosumab has demonstrated a superior, statistically significant, clinically meaningful, consistent and robust treatment effect for the reduction in the occurrence of SREs compared with zoledronic acid in breast, prostate and other solid tumours, across three Phase III RCTs. This represents the largest and most robust evidence package constructed to-date in SRE prevention in patients with bone metastases. Denosumab represents a medical step-change in the treatment of patients with bone metastases from solid tumours.

In the UK, based on NICE clinical guidelines and resulting bisphosphonate treatment patterns, when incorporating the PAS, denosumab represents a cost-effective treatment option for the prevention of SREs in the following patient groups:

- Breast cancer patients with bone metastases
- Prostate cancer patients with painful bone metastases who have experienced a prior SRE
- Other solid tumour patients with painful bone metastases who have experienced a prior SRE