Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Denosumab

Proprietary Product Name: Xgeva

Sponsor: Amgen Australia Pty Ltd

November 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	New Indication and New Strength
Decision:	Approved
Date of Decision:	29 August 2011
Active ingredient(s):	Denosumab (rch)
Product Name(s):	Xgeva
Sponsor's Name and Address:	Amgen Australia Pty Ltd
	115 Cotham Rd, Kew, VIC 3101
Dose form(s):	Solution for Injection
Strength(s):	70 mg/mL
Container(s):	Glass vial
Pack size(s):	1 vial and 4 vials
Approved Therapeutic use:	Prevention of skeletal related events in patients with bone metastases from solid tumours.
Route(s) of administration:	Subcutaneous (SC) injection
Dosage:	120 mg once every 4 weeks
ARTG Number (s)	175041

Product Background

Denosumab is currently registered as Prolia[1] for the treatment of osteoporosis in postmenopausal women. The recommended dosing regimen is a single 60 mg subcutaneous (SC) injection once every 6 months. The proposed new indication for denosumab is the prevention of skeletal related events in adults with advanced malignancies involving bone. The new proposed dose is 120 mg denosumab SC every 4 weeks. For the new indication, the sponsor is proposing to also register a new tradename, a new strength of the product and a new dosage regimen as described in Table 1.

[1] Prolia was recommended for approval by the Advisory Committee for Prescription Medicines (ACPM) at its February 2010 meeting.

Table 1. Comparison of Prolia and Xgeva

Indication	*Treatment of osteoporosis in postmenopausal women*	*Prevention of skeletal related events in patients with bone metastases from solid tumours*
Tradename	Prolia	Xgeva
Dose	60 mg SC	120 mg SC
Dose interval	Every 6 months	Every 4 weeks
Presentation	60 mg in 1 mL (60 mg/mL)	120 mg in 1.7 mL (70 mg/mL)

Bone metastases occur in more than 1.5 million patients with cancer worldwide[2] and are most commonly associated with cancers of the prostate, lung, and breast, with incidence rates as high as 75% of patients with metastatic disease.[3,4,5,6]

Irrespective of primary tumour type and their radiographic appearance, the underlying pathophysiology of bone metastases is locally increased pathological rate of bone remodelling, including increased osteoclast activity. This is associated with significant skeletal related events (SRE's), including fractures, radiation or surgery to bone, and spinal cord compression. In a study of women with advanced breast cancer and bone metastases, 64% of patients experienced at least 1 SRE and more than 50% of patients experienced pathologic fractures alone in the absence of bone protective therapies.[7]

A key objective in managing the skeletal morbidity associated with bone metastases is to inhibit excessive osteolysis and interrupt the cycle of bone destruction, tumour growth, and further bone destruction, thus preventing or delaying the skeletal complications. Currently, in addition to systemic anti tumour therapy, treatment with bisphosphonates is recommended and approved for patients with bone metastases in order to reduce the risk of developing SRE's. However, a significant number of patients continue to experience these complications, and an opportunity exists to improve the management of SRE's in this patient group.

Denosumab is a fully human immunoglobulin G2 (IgG2) monocloncal antibody with a targeted mechanism of action to inhibit receptor activator of nuclear factor kappa B ligand (RANKL). Accumulating evidence shows that tumour cells interact within the bone to stimulate the RANK-RANKL system, leading to cancer induced bone destruction. RANKL binds to RANK on osteoclasts or osteoclast precursors and acts as an essential factor in the formation, activation, and survival of osteoclasts, which is the sole type of cell responsible for bone resorption. Denosumab binds with high and specificity to the soluble and cell membrane-bound forms of

[2]Coleman RE, Brown JE. (2005). Monitoring Response to Treatment – the Role of Biomarkers. In: Jasmin C, Coleman RE, Coia L, *et al,* eds. Textbook of Bone Metastases. Hoboken, NJ: John Wiley and Sons; p105.
[3] Selvaggi G, Scagliotti GV. (2005). Management of bone metastases in cancer: A review. *Critical Reviews in Oncology/Hematology* 56:365-378.
[4] Carlin BI, Andriole GL. (2000). The natural history, skeletal complications, and management of bone metastases in patients with prostate carcinoma. *Cancer* 88:2989-2994.
[5] Coleman RE. (1997). Skeletal complications of malignancy. *Cancer* 80:1588-1594.
[6] Viadana E, Cotter R, Pickren JW, Bross IDJ. (1973). An autopsy study of metastatic sites of breast cancer. *Cancer Res.* 33:179-181.
[7] Lipton A, Theriault RL, Hortobagyi GN, *et al.* (2000). Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases. *Cancer* 88(5):1082-1090.

human RANKL. Consequently, inhibition of RANKL by denosumab has the potential to provide a targeted and effective means of reducing bone resorption and cancer-induced bone destruction.

At the time of this AusPAR there were four bisphosphonate agents registered in Australia for the treatment of advanced malignancies involving bone. Only zoledronic acid has a broad approval, the others being restricted to use in breast cancer or myeloma.

Regulatory Status

The Food and Drug Administration (FDA) approved Xgeva (denosumab) 120mg (70mg/ml) on 18th November 2010 for the indication "the prevention of skeletal-related events in patients with bone metastases from solid tumour" (same as approved Australian indication). Furthermore, the FDA requested the sponsor to conduct a clinical trial (rather than a nonclinical or observational study) to determine the safety of Xgeva 120 mg administered every four weeks by subcutaneous injection in patients with severe renal insufficiency (creatinine clearance less than 30 mL/min) and in patients receiving dialysis. The number of patients enrolled in the trial and the frequency and duration of plasma sampling will be sufficient to estimate the incidence and severity of hypocalcemia, hypomagnesemia, and hypophosphatemia in this patient population.

On 13th July 2011, the European Commission (EC) granted marketing authorization for XGEVA 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 tumors." The EC also granted XGEVA an additional year of data and market exclusivity in the EU since the indication was considered new for denosumab and based on the significant clinical benefit of Xgeva in comparison with existing therapies. The European public assessment report has been published.

An application to register Xgeva was submitted to Health Canada on the 14 May 2010 and approved on 10 May 2011 for the following indication:

> "For reducing the risk of developing skeletal related events in patients with bone metastases from breast cancer, prostate cancer, non-small cell lung cancer and other solid tumours. Xgeva is not indicated for reducing the risk of developing skeletal-related events in patients with multiple myeloma."

An application has also been submitted to SwissMedic on 12 July 2010 and a positive preliminary decision was issued on the 17 June 2011 for the following indication

> "Treatment of patients with bone metastases from solid tumours in combination with antineoplastic standard therapy."

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

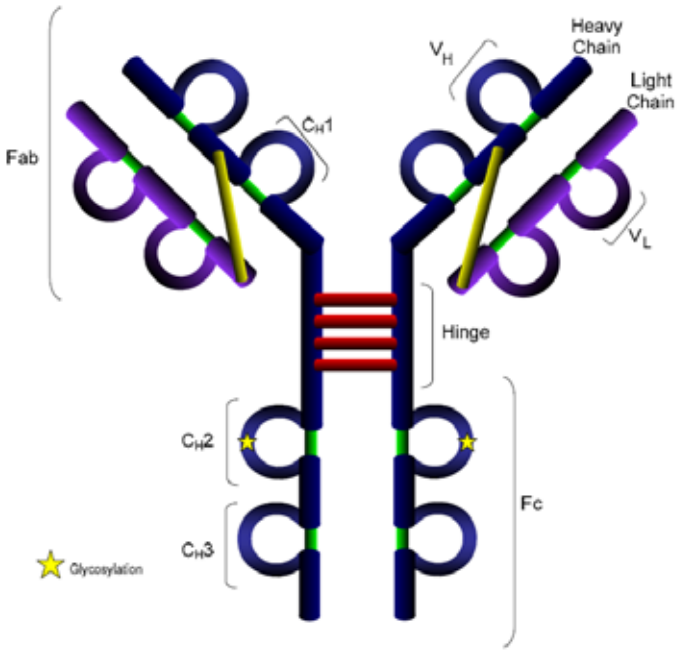
II. Quality Findings

Drug Substance (active ingredient)

Structure

Xgeva contains the same drug substance, denosumab, as that of the currently approved product Prolia. The structure of the drug substance is shown in Figure 1 below.

Figure 1. Denosumab structure.



Denosumab is a full-length human monoclonal antibody of the IgG2 subclass, consisting of two heavy chains and two light chains of the kappa subclass. Denosumab contains 36 cysteine residues, which are involved in both intrachain and interchain disulfide bonds. Each heavy chain contains an N-linked glycan at the consensus glycosylation site at asparagine 298. Each light chain contains 215 amino acids, with two intramolecular disulfides. Each heavy chain contains 448 amino acids with 4 intramolecular disulfides. The terminal lysine 488 is typically removed during cell culture.

Manufacture

Denosumab is derived from Xeno-mouse™ technology and produced in Chinese Hamster Ovary cells.

The denosumab drug substance manufacturing process consists of cell culture, harvest, recovery and purification. Cells from a single bioreactor are harvested by centrifugation followed by depth and membrane filtration and then purified to comprise a single batch of drug substance. The purification process consists of three chromatography steps, low pH viral inactivation, viral filtration, ultrafiltration/diafiltration (UF/DF) and drug substance fill. Cell banking processes were considered to be satisfactory.

All viral/prion safety issues have been addressed, including use of animal-derived excipients, supplements in the fermentation process and in cell banking.

Physical and Chemical Properties

The only product related impurities identified in denosumab drug substance are high molecular weight species (specifically dimers) and low molecular weight species which are routinely controlled at release.

Process related impurities include host cell DNA, host cell protein and other compounds derived from the manufacturing process. It has been adequately demonstrated that the purification process is capable of removing these impurities to acceptable levels.

Specifications

Appropriate validation data have been submitted in support of the test procedures for the proposed specifications which control identity, content, potency, purity and other biological and physical properties of the drug substance relevant to the dose form and its intended clinical use.

Stability

Stability data have been generated under real time and stressed conditions to characterise the stability/degradation profile of the substance and to establish a shelf life of the substance. The real time stability data support a shelf life of 36 months stored at -30°C in a polycarbonate container.

Drug Product

Formulation(s)

The drug product has the same composition as the drug substance. Denosumab drug product is supplied as a sterile, preservative free solution (70 mg/mL) intended for SC injection. The drug product is filled to a minimum deliverable volume of 1.7 mL with a target deliverable dose of 120 mg per vial. The product is supplied in two package size of 1 vial and 4 vials.

Manufacture

The 70 mg/mL drug product is undiluted from the source drug substance, thus there is no formulation step in the manufacturing process. The drug product is manufactured by drug substance pooling, sterile filtration, filling and inspection.

Specifications

Appropriate validation data have been submitted in support of the test procedures.

Stability

Stability data have been generated under real time and stressed conditions to characterise the stability profile of the product. Denosumab can be degraded by light. Stability of the product has been demonstrated under conditions that may be encountered during clinical use, including storage at room temperature (≤ 25°C), for a single period of up to 30 days, in the primary container, protected from light.

The real time stability data support a shelf life of 36 months stored at 5 ± 3° C.

Biopharmaceutics

Three biopharmaceutic studies (Reports 20050227, 20060286 and 20060446) which have been evaluated by the TGA previously were provided with the current Australian submission.

Quality Summary and Conclusions

The administrative, product usage, chemical, pharmaceutical and microbiological data submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

There were no quality issues raised.

III. Nonclinical Findings

Introduction

The new nonclinical data consisted of ten primary pharmacology studies and seven other studies. In addition, recent literature was also submitted. The sponsor clearly identified the newly submitted studies and made the changes needed to reflect the changes in animal:human exposure ratios that occur as a result of the new dosing regimen.

The sponsor commissioned ten primary pharmacodynamics studies, nine of which were conducted with osteolytic tumours and one with a mixed osteolytic/osteoblastic tumour. It would have been useful if the sponsor had conducted studies using osteoblastic tumours instead of relying on the limited published literature available. All of the sponsor studies were conducted using OPG-Fc (osteoprotegerin fused to the Fc portion of human IgG1). Osteoprotegerin contains a heparin binding domain and death domains, and binds to TRAIL, whereas denosumab does not. It would have been useful if the sponsor had conducted some studies with a murine version of denosumab. The published literature demonstrates that at least one murine RANK-Fc compound is available.

Pharmacology

Primary pharmacodynamics

RANKL is a member of the tumour necrosis factor (TNF) superfamily and is a key mediator in the pathway required for the formation, function, and survival of osteoclasts, the cells that resorb bone. Denosumab is a human IgG2 antibody that binds with high affinity and specificity to human RANKL, thereby neutralising the ligand and suppressing osteoclast-mediated bone turnover.

Traditionally, bone metastases from solid tumours are identified from their radiographic appearance. Bone lesions caused by multiple myeloma are primarily lytic, whereas breast cancer may cause lytic, mixed or osteosclerotic lesions and prostate cancer lesions are usually classified as osteosclerotic or osteoblastic. However, despite the radiographic appearance, histological evidence indicates that prostate cancer metastases form a heterogeneous mixture of osteolytic and osteoblastic lesions.

Histomorphometric analysis of metastatic lesions has shown that osteoblastic metastases form on trabecular bone at sites of previous osteoclastic resorption. The sponsor has argued that radiographic characterisations are simplistic, with dysregulation of the normal bone remodelling process occurring in all cancer-induced bone diseases. Clinical evidence to support this hypothesis includes a paper in which the marker for bone resorption N-telopeptide of type I collagen (NTX) was increased in all patients with bone metastases, whether they were lytic, blastic or mixed. A correlation has also been reported between NTX and clinical outcomes such as skeletal related events and survival (Sponsor's Nonclinical Summary). Thus, it would appear that the risk of skeletal complications and poor clinical outcome are partially dependent on the capacity to control the level of osteoclast activity and subsequent osteolysis.

Nonclinical evidence for the efficacy of denosumab produced by the sponsor relied on the use of the surrogate OPG-Fc (the natural RANKL inhibitor osteoprotegerin fused to the Fc portion of human IgG1). This was because denosumab only binds to human and primate RANKL, not to rodent RANKL. In order to compare the effects of OPG-Fc and denosumab in vivo, human RANKL knock-in mice were used. In these studies the effects of OPG-Fc and denosumab were shown to be similar, although not identical. It seems reasonable to use OPG-Fc as an indicator of how denosumab might be efficacious as a RANKL inhibitor, although toxicity would not be able to be assessed using OPG-Fc as a surrogate.

Unlike denosumab, OPG contains two death domains and a heparin binding domain and binds TRAIL (Tumour Necrosis factor-related Apoptosis-Inducing Ligand). TRAIL induces apoptosis in cells following binding to death receptors 4 and 5, including in cancer cells. Any in vivo binding of OPG to TRAIL would be expected to reduce apoptosis of the cancer cells. Thus, any effect of OPG binding to TRAIL would be expected to underestimate, not overestimate, the effect of denosumab on bone metastases.

OPG-Fc was effective at preventing osteoclast activity in SCID mouse models of human osteolytic cancers. For an osteolytic oestrogen receptor-negative breast cancer cell line, this resulted in a smaller tumour area as measured histologically, fewer tumour cells as measured with bioluminescence, increased animal survival and the prevention of new bone tumour formation. OPG-Fc also reduced overall tumour burden and histological tumour area for an oestrogen receptor-positive breast cancer cell line (that produces both osteolytic and osteoblastic tumours). For an osteolytic prostate cancer cell line the tumour area as judged by histology was reduced in the presence of OPG-Fc, but the overall tumour burden was only significantly decreased in the presence of docetaxel; however, the combination of docetaxel and OPG-Fc had a greater effect than docetaxel alone. Two osteolytic non-small-cell lung cell lines were investigated. One of these had significant decreases in tumour area as judged by histology, but the tumour burden as judged by bioluminescence was not significantly decreased. However, for the other non-small-cell lung cell lines both tumour area and tumour burden was decreased, with there being an additive effect with docetaxel treatment. In conclusion, in all of the osteolytic cell lines tested OPG-Fc decreased tumour size histologically, although in some cases the total tumour burden as judged by bioluminescence was not significantly decreased.

It is notable that the studies commissioned by the sponsor were mostly conducted with osteolytic cell lines, with one cell line (MCF-7) producing a mixture of osteolytic and osteoblastic tumours. The evidence for osteoblastic cell lines and for non-solid tumours (multiple myeloma) came from published papers. It appears as if some prostate cancers progress from osteoclastic to osteoblastic by changing the expression level of Dkk-1, a protein that increases RANKL expression and decreases OPG expression. RANKL inhibition by denosumab might counteract this change in phenotype. Two papers investigated the effect of RANK-Fc (the murine extracellular domain of RANK fused to human IgG1 Fc) on two different osteoblastic prostate cancer cell lines (Whang et al, 2005[8] and Zhang et al, 2003[9]). RANK-Fc was shown to be more effective against an osteolytic prostate cancer cell line compared to the osteoblastic cell line. In particular, RANK-Fc markedly decreased the number of limbs with tumours for the osteolytic cell line, but had no effect on this for the osteoblastic cell line. However, RANK-Fc did decrease the tumour area of the osteoblastic prostate cancer cell lines compared to controls.

[8] Whang PG, Schwarz EM, Gamradt SC, Dougall WC and JR Lieberman. The effects of RANK blockade and osteoclast depletion in a model of pure osteoblastic prostate cancer metastasis in bone. *J Orthopaedic Res* 2005; 23: 1475-1483.

[9] Zhang J, Dai J, Yao Z, Lu Y, Dougall W and ET Keller. Soluble receptor activator of nuclear factor [redacted] prostate cancer progression in bone. *Cancer Res* 2003; 63: 7883-7890.

The effect of RANK-Fc on a mixed osteoclastic and osteoblastic non-small-cell lung cancer was investigated in SCID mice. Treatment with RANK-Fc inhibited the formation of osteoclasts, led to a smaller tumour volume in bone and inhibited the lytic component of mixed lesion. However, inhibition of the blastic pathway by a different mechanism in addition to inhibition of the lytic pathway with RANK-Fc was necessary to effectively inhibit the progression of the mixed metastatic lesions in bone.

One published paper gave negative results for an osteolytic cell carcinoma when treated with OPG-Fc[10]. This tumour was a human lung squamous carcinoma cell line that produced a large amount of PTHrP (parathyroid hormone related protein; a hormone secreted by keratinocytes and other cell types). OPG-Fc decreased osteoclast numbers in the bones without the tumour, but was unable to block the effects of the locally high levels of PTHrP in the immediate vicinity of the tumour, leading to high osteoclast numbers and little effect of treatment on the tumour. These results indicate that denosumab may not be effective in the treatment of tumours that express high levels of PTHrP.

Bone marrow samples from multiple myeloma patients were shown to have increased RANKL expression and decreased OPG expression in areas that also possessed normal marrow. RANK-Fc was effective at preventing tumour bone resorption in SCID-hu mice that had received bone marrow cells from multiple myeloma patients. RANK-Fc was also effective at preventing hind limb paralysis and osteolytic lesions in a mouse model of multiple myeloma.

In conclusion, the nonclinical evidence is consistent with denosumab being efficacious for most osteolytic tumours (including multiple myeloma), although denosumab may not be effective for tumours that express high levels of PTHrP. There is less nonclinical evidence that denosumab is efficacious against osteoblastic tumours.

Secondary pharmacodynamics

The roles of RANK and RANKL in the immune system

Dendritic cells and osteoclasts share a common lineage, and both express RANK. RANKL is expressed on activated T and B cells as well as osteoblasts. These expression patterns have led to studies investigating the role of RANK and RANKL in immunomodulation.

Lymph nodes are completely absent in knockout mice lacking either RANK or RANKL, although these mice have intact splenic architecture and develop Peyer's patches normally (despite the presence of RANK in mature lymph nodes in the spleen and Peyer's patches) (Leibbrandt and Penninger, 2010[11]). Patients with various mutations in RANKL have no palpable lymph nodes, indicating that RANKL-RANK signalling also controls lymph node formation in humans. Studies indicate that RANKL and lymphotoxin ligands regulate lymph node genesis by controlling the colonisation and cluster formation of □4□7+CD45+CD4+CD3- cells during lymph node development.

RANKL has also been shown to be essential for the development of medullary thymic epithelial cells (mTECs) during embryogenesis, and RANK cooperation with another member of the TNF superfamily (CD40) is required in postnatal mice for thymic development (Akiyama *et al*, 2008[12]). mTECs are responsible for deletion of autoreactive T cells and thus for establishing

[10] Tennehill-Gregg SH, Levine AL, Nadella MVP, Iguchi H and TJ Rosol. The effect of zoledronic acid and osteoprotegerin on growth of human lung cancer in the tibias of nude mice. *Clin Exp Metastasis* 2006; 23:19-31.

[11] Leibbrandt A and JM Penninger. Novel functions of RANK(L) signalling in the immune system. *Adv Exp Med Biol*, 2010; 658: 77-94.

[12] Akiyama T, Shimo Y, Yanai H, Qin J, Ohshima D, Maruyama Y, Asaumi Y, Kitazawa J, Takayanagi H, Penninger JM, Matsumoto M, Nitta T, Takahama Y and J Inoue. The Tumor Necrosis Factor family receptors RANK and CD40 cooperatively establish the thymic medullary microenvironment and self-tolerance. *Immunity*, 2008; 29: 423-437.

immunological tolerance to self-proteins because they express a wide range of peripheral tissue-restricted self-antigens. It is unclear as to the relative involvement of CD40 and RANKL in the maintenance of immunological tolerance.

RANKL is expressed on $CD4^+$ and $CD8^+$ T cells, with high levels between 48 h and 96 h after activation. This RANKL binds to the RANK on the surface of dendritic cells and increases dendritic cell survival by anti-apoptotic pathways. Injection of mice with RANKL-treated dendritic cells resulted in increased primary and memory T cell responses. CD40 shows functional similarity to RANK in that it enhances the activation and survival of dendritic cells. However, CD40L expression on activated $CD4^+$ T cells peaks between 6 h and 8 hours post-activation, returning to resting levels 24h to 48 h post-activation. Thus, CD40L-CD40 probably primarily controls the initial priming stage of the immune reaction, whereas RANKL-RANK probably acts at later time points in the immune response.

Some antigens (such as proteins in adjuvants) predominantly use the CD40L-dependent pathway to activate T cells. However, other antigens (such as some viruses) use both a CD40L-dependent and an independent pathway (Bachmann *et al*, 1999[13]). CD40-deficient mice infected with either LCMV (lymphocytic choriomeningitis virus) or the influenza virus produced $CD4^+$ T cell responses that were reduced to almost zero in the presence of RANK-Fc (extracellular domain of RANK fused to human IgG1 Fc region). Thus, the RANKL pathway has a role in activating T cells in response to some antigens, although the degree of redundancy with CD40L is unclear.

The role of RANKL in B cell function is unclear. However, it has been shown that prostaglandin E2 treatment can increase the RANKL mRNA levels in $B220^+$ B cells in an oestrogen-dependent manner indicating that there may be a role for RANK in B cell function.

RANKL appears to mediate ultraviolet (UV) induced immunosuppression. RANKL expression in keratinocytes is upregulated following UV irradiation. These keratinocytes interact with Langerhans cells (dendritic cells in the skin) and the RANKL-RANK signalling increases the survival of the Langerhans cells which resulted in the Langerhans cells being more effective at enhancing the proliferation of regulatory $CD4^+CD25^+$ T cells. These regulatory T cells are a functionally distinct T cell population that maintain immunological self-tolerance. Thus, overexpression of RANKL in keratinocytes abrogated cutaneous contact hypersensitivity reactions.

$CD4^+CD25^+$ regulatory T cells have also been shown to be important in a mouse model of inflammation-induced Type 1 diabetes (Tet-TNF[redacted] mice with RANK-Fc (injection route unspecified) on postnatal day 21, 23 and 25 resulted in exacerbation of diabetes progression and a decrease in the proportion of islet-infiltrating haematopoietic cells that were $CD4^+CD25^+$ from 23% in the controls to 1%. Failure to generate $CD4^+CD25^+$ T cells also correlated with accelerated diabetes progression in the NOD mouse (a spontaneous model for autoimmune diabetes).

In conclusion, the nonclinical evidence clearly indicates that the RANK-RANKL interaction is involved in immunomodulation in a number of different animal models. $CD4^+CD25^+$ T cells have been implicated in a number of different studies. However, other subpopulations of T cells and B cells also express RANKL. The exact role of RANKL in the immune system and the degree of redundancy with other proteins is still unknown.

[13] Bachmann MF, Wong BR, Josien R, Steinman RM, Oxenius A and Y Choo. TRANCE, a Tumor Necrosis Factor family member critical for CD40 ligand-independent T Helper cell activation. *J Exp Med* 1999; 189: 1025-1031.

The effect of denosumab on the immune system

The effect of denosumab on the immune system was investigated in cynomolgus monkeys. No gross adverse effects were observed on the functioning of the immune system based on immunoglobulin levels, immunophenotyping of lymphocytes (CD3, CD4, CD8, CD16, CD20 and CD45), the T-cell dependent antibody response and/or the histopathology of lymphoid tissues in cynomolgus monkeys in the repeat-dose toxicity studies at exposures ≤15 times the clinical exposure or in a 16-month pharmacology study at exposures ≤10 times the clinical exposure (based on AUC). However, the lack of an overt effect could be misleading given that the laboratory animals under investigation would have been housed in a relatively protected environment and perturbations to the immune system may only be obvious in cases of extreme immunosuppression or immuno potentiation. Denosumab binds to monkey and human RANKL and prevents interaction with RANK. As described in the previous section, the RANK-RANKL interaction has some involvement in immunomodulation, in particular with a subset of CD4+CD25+ T cells, both peripherally and in the skin. Given the role of RANKL in the immune system, denosumab, which binds to RANKL, has the potential to interfere with this physiological function.

It is notable that immunophenotyping did not include CD25 and, thus, the effect of denosumab treatment on CD4+CD25+ T cells specifically has not been adequately investigated. Furthermore, the only deaths observed in the 12 month monkey study were in the high dose group, with mortalities attributable to infection by gastrointestinal protozoa (giardia and/or cryptosporidium). While it is acknowledged that protozoan infections occurred in all groups in this study, including the control groups, it cannot be discounted that a change in the immune system contributed to the deaths of the two high dose group monkeys.

An increased incidence of skin, urinary tract and endocardial infections in clinical trial subjects was an issue raised by the Delegate during deliberations on the previous Australian submission. There was also an increase in episodes of pancreatitis in denosumab-treated patients, with two of these episodes resulting in death. Although denosumab is clearly not a general immunosuppressant or immuno potentiator, the nonclinical evidence indicates that denosumab may have subtle immunomodulating activity, which may have contributed to the adverse events described above The risk of adverse events resulting from immunomodulation is likely to be greater with the increased dose and dosing frequency proposed for the new indication.

Angiogenesis

Conflicting data on the effect of RANKL inhibitors on angiogenesis has been obtained in both *in vitro* and *in vivo* models. The evidence is further complicated by OPG-Fc being used for some of the studies, as OPG-Fc does not just consist of a RANKL binding domain, but contains other functional domains as well. OPG-Fc is therefore not a good compound for investigating processes such as angiogenesis in which the role of RANKL is uncertain.

Further evidence for the role of RANKL and denosumab dosing in angiogenesis comes from RANK and RANKL knockout mice (which had no phenotypic change in vascular phenotype) and *in vivo* dosing of RANKL inhibitors in primates and in rodent cancer models. In repeat dose denosumab monkey studies there was no vascular abnormality, nor any preneoplastic or neoplastic lesions. In pharmacodynamic studies using OPG-Fc and human tumours dependent upon angiogenesis in SCID mice, OPG-Fc either reduced tumour progression or had a neutral effect. Considering all of the available evidence together, it is unlikely that denosumab treatment will have any effect on angiogenesis.

Cardiovascular effects

RANKL is expressed in vascular endothelial cells, and RANKL expression levels increase in calcified areas in both animals and patients. OPG knockout mice have moderate to severe vascular calcification, which can be rescued by overexpression of OPG. RANKL added to vascular smooth muscle cells induced matrix mineralization.[14] There was no vascular calcification or treatment-related vascular histopathology in monkeys dosed for up to 12 months with denosumab. Denosumab would be expected to have a neutral or beneficial effect on vascular calcification and atherosclerosis.

RANKL has also been shown to be involved in heart valve development in mouse and chicken embryos. This process consists of a proliferative phase followed by a remodelling phase. There is evidence that RANKL signalling is involved in the remodelling phase of heart valve development, in which the extracellular matrix is remodelled into highly organised trilaminar architecture.

Safety pharmacology

No new safety pharmacology studies were submitted with this application. This is considered acceptable for this application.

Pharmacodynamic interactions

The sponsor claimed that the specificity of denosumab for RANKL would indicate negligible pharmacodynamic interactions with other drugs including those used for chemotherapy and hormone therapy. This argument seems reasonable. A number of the primary pharmacology studies conducted by the sponsor using OPG-Fc were conducted in combination with either tamoxifen or docetaxel. In these studies an additive effect was observed with the combination group. No untoward effects were observed on the pharmacodynamic activity of alendronate or denosumab in a therapeutic switch study in monkeys. The extent of the nonclinical investigation of drug-drug interactions is acceptable. Evidence for the safety of use of denosumab with other drugs relies on clinical data.

Pharmacokinetics

No new nonclinical pharmacokinetic studies with denosumab were conducted in this application. Absorption of denosumab into the systemic circulation after SC administration was slow in all species, with peak serum concentrations achieved at 72 h post-dose in mice, rats, monkeys and, at 1-4 weeks, in humans. In mice and rats (species in which denosumab does not bind to RANKL) the intravenous (IV) pharmacokinetics of denosumab were linear over the dose range 0.1 to 10 mg/kg and serum half-life was very long, approximately 19 days in mice and 11 days in rats. In huRANKL knock-in mice, the exposure and half-life were both significantly reduced (circa 5-6 fold) compared to wild-type mice, indicating that binding to RANKL increases clearance of the antibody. In cynomolgus monkeys (a species in which denosumab binds to RANKL) both the IV and SC pharmacokinetics were non-linear over the dose range 0.0016 to 1 mg/kg (with clearance markedly higher [up to ~16-fold] at the lower doses) but approximately linear at higher doses (≤50 mg/kg SC). The finding is consistent with binding of denosumab to RANKL leading to saturable accelerated elimination. After a single dose, serum concentrations followed a tri-phasic pattern, with a rapid distribution phase (2 days after IV administration and 4 days after SC), a slower dose-dependent phase and a rapid terminal phase (after 10 days for IV administration and 7 days for SC). Exposure was massively reduced in animals that developed anti denosumab

[14] Panizo S, Cardus A, Encinas M, Parisi E, Valcheva P, López-Ongil S, Coll B, Fernandez E and JM Valdivielso. RANKL increases vascular smooth muscle cell calcification through a RANK-BMP4 dependent pathway. *Circ Res* 2009; 104: 1041-1048.

antibodies (for example, the maximal plasma concentration (C_{max}) and the area under the plasma concentration time curve (AUC) at 50 mg/kg were reduced by more than 20- and 100-times, respectively, in antibody-positive monkeys in the 12-month toxicity study). Serum half-life of denosumab in humans at 60 mg SC was reported to be 25-27 days.

The volume of distribution was low in all three nonclinical species (mouse, rat and cynomolgus monkey), indicating a lack of significant extravascular distribution. This was reflected in the tissue distribution studies with radioactive iodine (^{125}I) denosumab in the monkey. Although tissue distribution of radioactivity was wide, peak concentrations in tissues were all below that for serum, except for at the injection site and the thyroid. Tissues with high radioactivity concentrations included the inguinal and axillary lymph nodes, the spleen and the ovaries. Radioactivity was not distributed to the spinal cord or the brain. No specific uptake in bone was seen (peak levels of radioactivity in bone and bone marrow were ≤12% of the serum C_{max}). Most (>85%) of the serum radioactivity was Trichloracetic acid (TCA) precipitable and therefore likely to represent intact antibody. No conventional metabolism studies were submitted; this is acceptable for a protein drug as degradation to small peptides and individual amino acids is expected. Excretion of ^{125}I-denosumab-derived radioactivity following SC dosing in monkeys was predominantly via the urine (76–95%), and principally in the form of small peptides or free iodide.

Pharmacokinetic interactions

Pharmacokinetic interactions with other drugs are not expected. Neither RANK nor RANKL are constitutively expressed on human hepatocytes, so regulation of hepatic CYP expression by binding to hepatocyte membranes is unlikely.

Relative exposure

Exposure ratios have been calculated based on animal: human AUC values adjusted for dosing frequency. Calculations are made with reference to a human value of 723,000 ng·day/mL (17.35 mg.h/mL) for the mean area under the plasma concentration time curve over the 4-week dosing interval ($AUC_{0-\tau}$), obtained after the fifth 120 mg SC dose (the proposed clinical dose) in Study 20040113. The C_{max} at this dose was 27.1 µg/mL and the accumulation ratio from the first to the fifth dose was 2.52. Relative exposure in the nonclinical dose studies are tabulated in Tables 3 and 4 below.

Table 3. Relative exposure in repeat-dose studies

Study	Species	Duration	Dosing frequency	Route	Dose[1] (mg/kg)	$AUC_{0-\tau}$ (mg·h/mL)	Exposure ratio[2]
101447	**Monkey** Cynomolgus	1 month	Once weekly	SC	0.1	0.349	0.08
					1	3.41	0.8
					10	42.0	9.7
				IV	**10**	68.6	16
102090		6/12 months	Once monthly	SC	10	48.2	2.8
					50	268	15
103981		16 months	Once monthly	SC	25	101	5.8
					50	171	9.9

[1] NOAEL shown in bold text.

[2] Based on a human $AUC_{0-\tau}$ of 17.352 mg·h/mL (= 723 µg·day/mL), obtained at the proposed clinical dose (120 mg Q4W) in Study 20040113; animal:human AUC values are compared following multiplication of the animal AUC values by 4 (for once-weekly administration) or 1 (once-monthly administration) to account for the higher dosing frequency employed in the animal studies compared with the 4-weekly administration in humans.

Table 4. Relative exposure in reproductive toxicity studies

Study	Species	Dosing frequency	Route	Dose[1] (mg/kg)	$AUC_{0-\tau}$ (mg·h/mL)	Exposure ratio[2]
102843 *Female fertility*	**Monkey** Cynomolgus	Once weekly	SC	2.5	4.22	1.0
				5	16.4	3.8
				12.5	67.8	16
102842 *Embryofetal development*		Once weekly (over GD20–50)	SC	2.5	8.80	2.0
				5	15.5	3.6
				12.5	41.0	9.5

AUC data for the embryofetal development study are for animals negative for neutralising antibodies.

[1] NOAEL is shown in bold text.

[2] Based on a human $AUC_{0-\tau}$ of 17.352 mg·h/mL (= 723 µg·day/mL), obtained at the proposed clinical dose (120 mg Q4W) in Study 20040113; animal:human AUC values are compared following multiplication of the animal AUC values by 4 (for once-weekly administration) or 1 (once-monthly administration) to account for the higher dosing frequency employed in the animal studies compared with the 4-weekly administration in humans.

Toxicology

General toxicity

As denosumab is not pharmacologically active in rodents, cynomolgus monkeys were selected for the evaluation of repeat-dose and reproductive toxicity. The repeat-dose toxicity of denosumab in cynomolgus monkeys was examined following weekly SC or IV administration for one month at doses up to 10 mg/kg, or monthly SC administration for 12 months at doses up to 50 mg/kg. It was considered that the studies were appropriately designed and conducted.

There was little evidence of toxicity, and changes that were noted were related to the pharmacological effects of denosumab. Clinical chemistry, haematology and urinalysis parameters showed no significant changes indicative of toxicity. Decreased serum alkaline phosphatase (ALP) activity is consistent with other changes in bone metabolic markers, namely decreases in serum or urinary N-telopeptide, and serum osteocalcin and calcium, which reflect inhibition of bone turnover. Gross and microscopic pathological examinations did not reveal any treatment-related effects except in the bone tissue (decreased chrondroclasis, enlarged epiphyseal growth plate/symphysis sternalis and decreased osteoclasts and osteoblasts at ≥10 mg/kg/month SC), which reflected the pharmacological activity of denosumab. Anti-denosumab antibodies (both binding and neutralising) developed in 55% of treated animals in the 12 month study, but the incidence decreased with increasing dose and was quite low at the high dose level (2/15 animals); serum concentrations of denosumab were sufficient to achieve the pharmacodynamic response, and exposure (based on Cmax and AUC) increased in a dose related manner. Mortality from infection occurred in 2/16 animals in the 50 mg/kg dose group in the 12 month study, and this is discussed above under the heading "The effect of denosumab on the immune system." In addition, thyroid weight increased in female monkeys after 4 weeks of receiving 10 mg/kg/week denosumab IV (unaccompanied by histopathological changes), although this was not reproduced in a second study with comparable exposure but longer duration (50 mg/kg/month SC for 12 months). The 12-month study established a No Observable Adverse Effect Level (NOAEL) of 50 mg/kg SC for once monthly administration, a dose yielding 15-times the clinical exposure to denosumab at the proposed dose for the new indication (based on AUC; see table above).

Genotoxicity and carcinogenicity

No genotoxicity or carcinogenicity studies have been conducted. Given that denosumab is a biotechnology derived pharmaceutical not expected to interact directly with DNA or other chromosomal material, and that there were no proliferative lesions observed in the repeat-dose toxicity studies, this is considered acceptable and is consistent with the relevant European Union guideline adopted by the TGA[15]. Furthermore, rodent carcinogenicity studies would be inappropriate due to the animals' lack of pharmacodynamic responsiveness to denosumab.

Reproductive toxicity

No new reproductive toxicity studies were submitted with this application. This is considered acceptable given that the pregnancy category of D is being retained.

Developmental toxicity

The sponsor submitted four studies in neonatal rats. Three of these studies involved administration of OPG-Fc to neonatal rats. One of these studies included murine RANK-Fc and two studies included alendronate. The fourth study used transgenic rats that expressed OPG constitutively. In the transgenic rats, OPG plasma levels were significantly increased, but were not as high as in the rats that received OPG-Fc treatment. In the transgenic rats there was no effect on tooth eruption or body weight, but osteoclastogenesis was clearly inhibited and bone properties were altered. In the OPG-Fc treated rats femur length was significantly reduced, tooth eruption was delayed or prevented and tooth development was altered. Body weight was lower in the OPG-Fc treated groups, and this did not appear to be entirely due to the difficulty in eating pelleted food with fewer teeth, because a lower body weight was also observed when powdered food was provided. A recovery study was conducted, in which a ten week recovery

[15] Note for Guidance on Preclinical Safety Evaluation of Biotechnology Derived Pharmaceuticals. CPMP/ICH/302/95. http://www.tga.gov.au/pdf/euguide/ich030295en.pdf

period followed 6 weeks of treatment to rats, starting at 2 weeks of age. In this study there was some recovery of bone parameters and tooth eruption, but the recovery was only partial.

Use in children

The proposed indication is for the treatment of adults. Denosumab treatment of paediatric populations carries potential risks of reduced bone growth and delayed tooth eruption, with the possibility of altered tooth development.

Local tolerance

No specific studies were submitted. There was no evidence of treatment related irritation at the injection sites in the studies conducted.

Benefit-risk assessment

The nonclinical evidence indicates that for most osteolytic cancers denosumab is likely to be efficacious. The risks identified were associated with exaggerated pharmacological effects. However, the pharmacology of RANKL is not limited to the bone but also involves various developmental processes and the immune system. No additional risks have been identified in the newly evaluated nonclinical data. Given that this treatment is for patients with advanced malignancies, the nonclinical data indicate that the benefits of the proposed denosumab treatment to these patients are likely to outweigh the risks.

Nonclinical Summary

- The new nonclinical data consisted mainly of primary pharmacology data and studies of tooth eruption and bone development in neonatal rats.
- Denosumab is a specific inhibitor of RANKL and prevents RANKL binding to its receptor RANK. All of the effects of denosumab are likely to be a result of this inhibition. The RANK/RANKL signalling system is involved in both osteoclast/osteoblast communication and in signalling within the immune system.
- Denosumab does not bind to murine RANKL and therefore all of the primary pharmacology studies submitted by the sponsor used osteoprotegerin-Fc (OPG-Fc) instead of denosumab. Of the ten studies submitted, nine were conducted with osteolytic cell lines and one with a mixed osteolytic/osteoblastic cell line. Studies from the literature provided nonclinical evidence about the effect of RANK-Fc (a murine version of denosumab) in osteoblastic cell lines and multiple myeloma.
- The nonclinical evidence is consistent with denosumab being efficacious for most osteolytic tumours (including multiple myeloma) There is less nonclinical evidence that denosumab has efficacy against osteoblastic tumours.
- The RANK-RANKL interaction is involved in immunomodulation in a number of different animal models. RANKL is expressed on a number of T and B cells, and $CD4^{+}CD25^{+}$ T cells have been shown to be regulated by the RANK-RANKL signalling system. However, the exact role of RANKL in the immune system and the degree of redundancy with other proteins is still unknown. Denosumab, as an inhibitor of RANK-RANKL signalling, has the potential to be an immuno modulator.
- Considering all of the available nonclinical evidence together, it is unlikely that denosumab treatment will have any effect on angiogenesis.
- No new safety pharmacology, nonclinical pharmacokinetics, repeat dose toxicity, genotoxicity, carcinogenicity or reproductive toxicity studies were submitted with this application. This is considered acceptable.

- Pharmacodynamic interaction studies were conducted with docetaxel and tamoxifen in primary pharmacology studies, and a therapeutic switch study was conducted with alendronate in monkeys. The specificity of denosumab for RANKL makes it unlikely that pharmacodynamic interactions will occur with other drugs. Pharmacokinetic interactions with other drugs are not expected. Evidence for safety of use with other drugs relies on clinical data.
- Four studies in neonatal rats investigated the effect of the RANKL binding protein OPG-Fc or OPG on bone and tooth parameters. RANKL inhibition resulted in lower body weight, changes to bone parameters and delayed tooth eruption. Recovery was only partial.
- There was no evidence of treatment-related irritation at the injection sites in the studies conducted.
- There are no nonclinical objections to the registration of denosumab with the proposed dosing regimen for the proposed indication.

Conclusions and Recommendations

The nonclinical evidence is consistent with denosumab being efficacious for most osteolytic tumours (including multiple myeloma) There is less nonclinical evidence that denosumab is efficacious against osteoblastic tumours.

The RANK-RANKL interaction is involved in immunomodulation, and thus denosumab has the potential to act as an immuno modulator. When commenting on the previous application, the Delegate raised the issue of an increase in infection related to organs such as the skin, urinary tract and endocardium in denosumab-treated patients in the clinical trials. In addition, there was an increase in episodes of pancreatitis in denosumab-treated patients, with two episodes in denosumab-treated patients resulting in death. Whether the potential for denosumab to act as an immuno modulator is related to any or all of these observations is unknown.

Studies in neonatal rats indicate that possible effects of denosumab on bone growth and tooth eruption in children may only be partially reversible.

Given that this treatment is for patients with advanced malignancies, the nonclinical data indicate that the benefits of the proposed denosumab treatment to these patients are likely to outweigh the risks. There are no nonclinical objections to the registration of denosumab with the new dosage regimen for the proposed indication.

The sponsor provided a response to the nonclinical report and it has been included under the heading "*Response from Sponsor*" below on pages 116-120."

IV. Clinical Findings

Introduction

The denosumab clinical development program for the treatment of adult patients with advanced malignancies involving bone to prevent skeletal related events (SRE) consists of 8 studies in total. Three pivotal multinational, randomized, double-blind, active-controlled Phase III studies have been conducted in adult subjects with malignancies involving bone. Study 2005-0136 involved patients with advanced breast cancer and bony metastases (n=2046); Study 2005-0103 recruited men with hormone refractory (castrate resistant) prostate cancer and

bone metastases (n=1901) and Study 2005-0244 involved subjects with various solid tumours (excluding breast and prostate cancer) and bony metastases or multiple myeloma (n=1901). The three pivotal Phase III studies were similar in design, endpoints and statistical analysis. All studies assessed whether denosumab was non-inferior (primary efficacy endpoint) or superior (secondary efficacy endpoint) to zoledronic acid in delaying the time to first and subsequent SRE. The study designs were discussed with regulatory bodies in Europe and USA prior to commencement. Subjects in each of the studies were randomized 1:1 to receive either denosumab 120 mg SC every 4 weeks or zoledronic acid 4 mg IV every 4 weeks (with matching placebo to maintain blinding). The dose and choice of zoledronic acid as the active comparator was appropriate because it is considered the standard of care and is licensed for use in several malignancies involving bone. Of note, patients with a creatinine clearance of less than 30 mL/min were excluded because of restrictions on the use of zoledronic acid, and daily supplements of at least 500 mg of calcium and at least 400 IU of vitamin D were recommended (unless the subject was hypercalcaemic). The primary blinded treatment phase for each of the three pivotal studies was the date until approximately 745 subjects were anticipated to have experienced a SRE. Results of an approximately 4 month extended blinded treatment phase were also included for Studies 2005-0136 and 2005-0244..

The submission also contained the interim safety report (no efficacy data) from another Phase III study (2005-0147) which involved 1435 men with histologically confirmed, hormone refractory prostate cancer who had been chemically or surgically castrated and had a total serum testosterone of less than 50 mg/dL (1.72 nmol/L). The subjects are at high risk of developing bone metastasis and needed evidence of a rising PSA to be included.

Two open-label Phase II studies (2005-0134 and 2004-0215) also provided supportive safety data for the indication in advanced malignancy. Study 2005-0134 involved 96 denosumab treated patients with relapsed (n=53) or plateau phase (n=43) multiple myeloma who were actively treated until disease progression (expected to be at least 6 x 28 cycles of therapy, 168 days) or withdrawal. Study 2004-0215 recruited 37 adult subjects with histologically confirmed giant cell tumour of the bone who all received denosumab 120 mg SC every 4 weeks (with loading dose on Days 1, 8 and 15) until either complete tumour resection, disease progression or discontinuation.

A further two Phase II dose-ranging studies: Study 2004-0113 (female subjects with breast cancer and no prior bisphosphonate exposure) and Study 2004-0114 (men or women with various solid tumours [excluding lung cancer] or multiple myeloma receiving IV bisphosphonate for bone metastases) contributed data as part of the pharmacology, efficacy and safety sections of the current Australian submission.

Additional elements which required evaluation in the current submission:

- Two pharmacokinetic studies in adult patients with bone metastases (Studies 2001-0123 [8 centres in Britain, Europe and USA] and 2004-0176 [Japanese subjects]),
- Two population pharmacokinetic reports (111914 [various subject groups] and 112014 [adult patients with malignancy]),
- Two integrated analyses for subjects with cancer (efficacy and safety), and
- Immunogenicity overview for patients with advanced malignancy.

All studies in the denosumab clinical development program were conducted in accordance with the principles of Good Clinical Practice (GCP) and compliance with ethical requirements was met. Protocol deviations involved <10% of subjects in all three pivotal Phase III trials, were clearly articulated and were equally distributed among the active and control treatment groups.

Pharmacokinetics

Introduction

Two Phase I pharmacokinetic (PK) trials (2001-0123, 2004-0176) in patients with bone metastasis provide the key PK data for the current Australian submission. Supportive PK data was provided from further Phase II studies (outlined in detail in the *Pharmacodynamic* section) and the pivotal Phase III trials. This submission included two population analyses: a population PK report in a heterogeneous population of adults (Study 111914) and a population PK/PD in patients with cancer (Study 112014; primarily discussed in the PD section). Preliminary analysis from two further studies for indications different to this submission (Study 2004-0215 [a Phase II treatment for treatment of giant cell tumour of bone] and 2005-0134 [a Phase II treatment of relapsed or plateau-phase multiple myeloma (MM)]) have also been provided by the sponsor with limited PK and PD data available. Results from these studies are similar to other trials and therefore these additional studies will not be specifically discussed here.

The new PK trials address the new proposed indication and variations in posology. Previous evaluations for this product included four healthy volunteer PK trials and one PK trial in adult patients with chronic renal impairment.

Study 2001-0123 was a Phase I, single dose, randomised, double-blind, active-controlled trial comprising a dose escalation and parallel-dosing phase. In total, 29 patients with breast cancer and 25 subjects with MM were involved. Subjects were randomised to receive either denosumab 0.1, 0.3, 1.0 or 3.0 mg/kg SC or pamidronate IV in the dose escalation phase; denosumab 0.1, 0.3, and 1.0 mg SC in the breast cancer parallel-dosing phase; and denosumab 3.0 mg/kg SC or pamidronate IV in the MM parallel-dosing phase. All except three subjects were Caucasian with a mean age of 55 (standard deviation (SD) 9.7) and 60 (9.4) years in the denosumab breast cancer and MM strata, respectively. The corresponding mean weights were 74 kg (range 56-104 kg) and 75 kg (44-108 kg) for the two denosumab treated strata, respectively. In both phases, intense PK sampling occurred up to Day 85.

Study 2004-0176 was a Phase I, open-label, single and multiple-dose escalation study in Japanese subjects with breast cancer and at least 1 bone metastasis. Subjects sequentially received denosumab SC either as a single dose of 60 mg, a single dose of 180 mg, or three doses of 180 mg fourth weekly. Intense PK sampling occurred up to study Day 85 for the single dose cohorts. In the third dose cohort, limited PK sampling was performed up to Day 29 and Day 141 after the first and last dose, respectively.

A summary of all the trials with PK data, including those previously evaluated is found in Table 5.

Table 5. Denosumab Clinical Pharmacology Study Characteristics

Study	Healthy Volunteers	Patients	Initial PK/ Tolerability	Intrinsic Factor PK	Extrinsic Factor PK	PD	PK Sampling[b]
Healthy Volunteer Pharmacokinetics and Initial Tolerability							
20010124	☐		●			☐	intense
20030148	☐		●			☐	intense
20030164	☐		●			☐	intense
20030180	☐		●			☐	intense
Patient Pharmacokinetics and Initial Tolerability (Advanced Cancer)							
20010123		☐	●			☐	intense
20040176		☐	●			☐	intense & limited[c]
Intrinsic Factor Pharmacokinetics							
20040245	☐[d]			●		☐	intense
Extrinsic Factor Pharmacokinetics[e]							
20040114		☐			●	☐	limited
Other Studies Contributing Pharmacokinetic and Pharmacodynamic Data							
Biopharmaceutics Studies[f]							
20050227	☐		☐			☐	intense
20060286	☐		☐			☐	intense
20060446	☐		☐			☐	intense
Dose-ranging Studies in the Prevention of SREs							
20040113		☐			●	☐	limited
Safety and Efficacy Studies in the Prevention of SREs							
20050136		☐			●	☐	sparse
20050244		☐				☐	sparse
20050103		☐				☐	sparse
Safety and Efficacy Studies in Other Indications							
20040215		☐				☐	sparse
20050134		☐				☐	sparse

(●) primary clinical pharmacology category; (☐) provides specified clinical pharmacology data;
PD = pharmacodynamics; PK = pharmacokinetics; SREs = skeletal-related events

[a] The organogram of all clinical studies in this marketing application is provided in Figure 63.

[b] intense = ≥ 9 samples collected after at least 1 dose; limited = 3 to 8 samples collected after at least 1 dose; sparse = trough and < 3 samples collected after at least 1 dose

[c] intense sampling for single dose cohort and limited sampling for multiple dose cohort

[d] healthy volunteers and subjects with kidney disease

[e] assessed effects of previous bisphosphonate treatment and concomitant treatment with chemotherapy or hormone therapy on denosumab PK and PD

[f] described in Module 2.7.1 of this marketing application

Methods

Serum denosumab concentrations were measured with a conventional sandwich enzyme-linked immunosorbent assay (ELISA) following a validated procedure. The range, accuracy and precision of the assay are reported appropriate for the dosing range studied.

For both the Phase I PK studies, intense PK sampling occurred out to Day 85 after a single dose. Given the long-half life of denosumab, this sampling design is insufficient to capture full AUC data profile, particularly at the higher doses. However, near complete AUC curves are available from the previous studies involving healthy volunteers. All evaluated trials were randomised parallel studies, and hence washout periods are not relevant. Non-compartmental analysis was performed for the relevant PK studies.

Population PK Analysis

A population PK (popPK) analysis (**Study 111914**) was performed using a non-linear mixed effects model in NONMEM (versions 6 and 7). The combined dataset comprised nine Phase I studies (2001-0123, 2001-0124, 2003-0148, 2003-0164, 2004-0176, 2005-0227, 2005-0241, 2006-0286, and 2006-0446), six Phase II studies (2001-0223, 2004-0113, 2004-0114, 2004-0215, 2005-0134, and 2005-0172) and five Phase III studies (2003-0216, 2004-0132, and 2004-0135 with Studies 2005-0244 and 2005-0136 used as an external validation set). The popPK dataset included a heterogeneous group of adult subjects including healthy volunteers, post menopausal women with osteopenia or osteoporosis and subjects with cancer.

A two compartmental model with first order distribution to the peripheral compartment and parallel linear and non-linear elimination described the data. To account for subcutaneous dosing, first order absorption and bioavailability (F) was included. All parameters were assumed log-normally distributed. Covariates included in the final model were allometrically scaled body weight, age, race, underlying disease state and treatment with aromatase inhibitors.

Absorption

In both of the Phase I PK studies involving subjects with cancer, C_{max} increased in a dose-proportionate manner with a 4 fold increase seen in C_{max} over the 3 fold examined dose range (60 mg to 180 mg) in Study 2004-0176. The median time of maximal plasma concentration (T_{max}) was 8-10 days after a single dose and 14-18 days with fourth weekly dosing.

Subcutaneous bioavailability was previously evaluated in a healthy subject trial only, but ranged from 35-85%. Likewise, relevant bioequivalence studies have been previously evaluated by TGA.

The population PK analysis (Study 111914) found subcutaneous bioavailability to be 62% (constant over the dose range). Mean absorption half-life was 3.14 days.

Distribution

The popPK Study 111914 found values for the volume of distribution of 2.66L/66 kg centrally and 1.3L/66 kg peripherally. These values are in keeping with the one previous healthy subject trial where IV dosing was included and suggest that denosumab is not widely distributed outside of the vasculature.

Elimination

Having a high molecular weight (150 kDa), denosumab is not compatible with renal excretion. Having a composition similar to endogenous immunoglobulins, denosumab is unlikely to be eliminated via hepatic metabolism. It is likely to be cleared through endogenous immunoglobulin clearance pathways.

The popPK Study 111914 utilized a structural model with a saturable (non-linear) component [representing a free RANKL-mediated elimination] and a non-saturable (linear) component [representing non-specific reticuloendothelial system elimination]. This structural model was found to best describe the non-linear PK of denosumab.

Mean beta-phase half-life ranged from 25-35 days (Studies 2004-0176 and 2004-0113). Observed steady-state was noted after the sixth dose (fourth weekly dosing).

Dose proportionality and time dependency

In keeping with results from healthy volunteers, non-linear PK was demonstrated in subjects with breast cancer and multiple myeloma (Study 2001-0123), particularly for the lower doses (<1.0 mg/kg). In breast cancer subjects a 25 fold increase in AUC was seen between doses of 0.1 and 1 mg/kg. Similarly, a 4.6 fold increase in AUC was seen for doses between 1 and 3 mg/kg. Subjects with multiple myeloma had a 22 fold increase in AUC at lower doses and a 1.8 fold increase in AUC with the higher doses. Within the range of proposed dosing of denosumab (>1 mg/kg), AUC increased approximately dose proportionally but considerable inter subject variability was seen (Studies 2004-0176 and 2004-0113).

No evidence of time dependency was identified in any of the Phase I, Phase II or popPK studies with dose accumulation consistent with expectations.

Intra- and inter-individual variability

Significant inter individual PK variability was seen in the clinical studies. Summary variables, with between subject variability estimates from the popPK analysis are provided in Table 6. Inter individual variability coefficients of variance for the various PK parameters range from 34%-53%.

Table 6. Summary PK Variables and Between Subject Variability (popPK Study 111914)

Parameters	Units	Typical Value	Factor [b]	95%CI
Linear Clearance (CL) [a]	mL/hr/66kg	3.08		2.97 - 3.18
- Multiple Myeloma		-	1.71	1.68 - 1.74
- Breast Cancer		-	1.15	1.11 - 1.2
- Aromatase Inhibitors Therapy		-	0.795	0.714 - 0.876
- Prostate Cancer		-	1.30	1.14 - 1.46
- Giant Cell Tumor		-	1.28	1.15 - 1.41
- Other Solid Tumors		-	1.39	1.38 - 1.39
- Black		-	1.21	1.12 - 1.3
- Hispanic		-	1.24	1.17 - 1.31
Central Volume (V_c) [a]	mL/66kg	2660		2540 - 2770
- Black			0.91	0.792 - 1.03
Inter-compartmental Clearance (Q) [a]	mL/hr/66kg	39.5	-	37.8 - 41.2
Peripheral Volume (V_p) [a]	mL/66kg	1300	-	1280 - 1330
Absorption Rate (k_a) [a]	1/hr	0.00921	-	0.00859 - 0.00982
- Age power [c]		-0.556	-	-0.658 – (-0.454)
- Reference Age [c] (AGE_{ref})	years	69.8	-	60.4 - 79.1
Bioavailability (F_{SC})	%	62.1	-	60.5 - 63.7
Baseline RANKL Concentration (R_{max})	ng/mL	590	-	564 - 617
Quasi-Steady-State Constant (K_{SS})	ng/mL	185	-	173 - 198
RANKL Degradation Rate (k_{deg})	1/hr	0.00148	-	0.00142 - 0.00153
Complex Internalization Rate (k_{int})	1/hr	0.00651	-	0.00618 - 0.00684
Between Subject Variability (Variance [CV%])				
Linear Clearance (ω^2_{CL})		0.115 [CV=34.0%]	-	0.108 - 0.123
Clearance-Volume Correlation [R] (ω_{CL} ω_{Vc})		0.0857 [R=0.559]	-	0.0763 - 0.0951
Central Volume (ω^2_{Vc})		0.204 [CV=45.2%]	-	0.188 - 0.22
Baseline Target Concentration (ω^2_{Rmax})		0.19 [CV=43.6%]	-	0.172 - 0.209
Absorption Rate (ω^2_{Ka})		0.279 [CV=52.8%]	-	0.257 - 0.301

Page 1 of 2

[a] For a typical subject: 66 kg, 70 years of age, healthy, white
[b] Magnitude of the covariate effect: factor by which the typical value is multiplied
[c] Absorption rate declined with age. The multiplicative factor was $(Age/AGE_{ref})^{Age\ Power}$ up to $Age=AGE_{ref}$ and remained constant at $Age > AGE_{ref}$

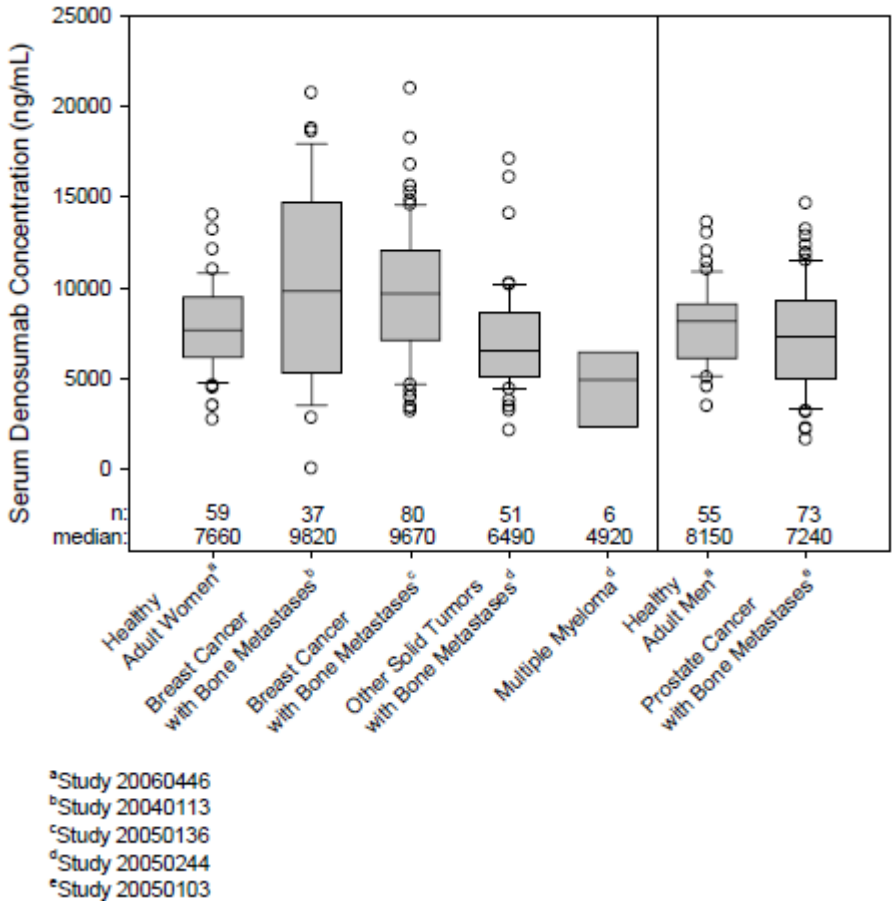
Pharmacokinetics in target population

In general, patients with advanced cancer demonstrated comparable PK characteristics with healthy subjects. Where variability was observed, it was generally below the degree of unexplained inter-individual subject variability.

In Study 2001-0123, breast cancer subjects had lower AUC (~50%) than MM subjects at doses between 0.1 and 1 mg/kg. At doses of 3 mg/kg, AUC was similar up to Day 28 and then higher in breast cancer subjects up until Day 84 (the last day of sampling in this trial). Figures 2 and 3 demonstrate comparative 1 and 3 month trough denosumab concentrations from the relevant PK trials. The six month box-plot is not provided here but is similar to that observed at 3 months.

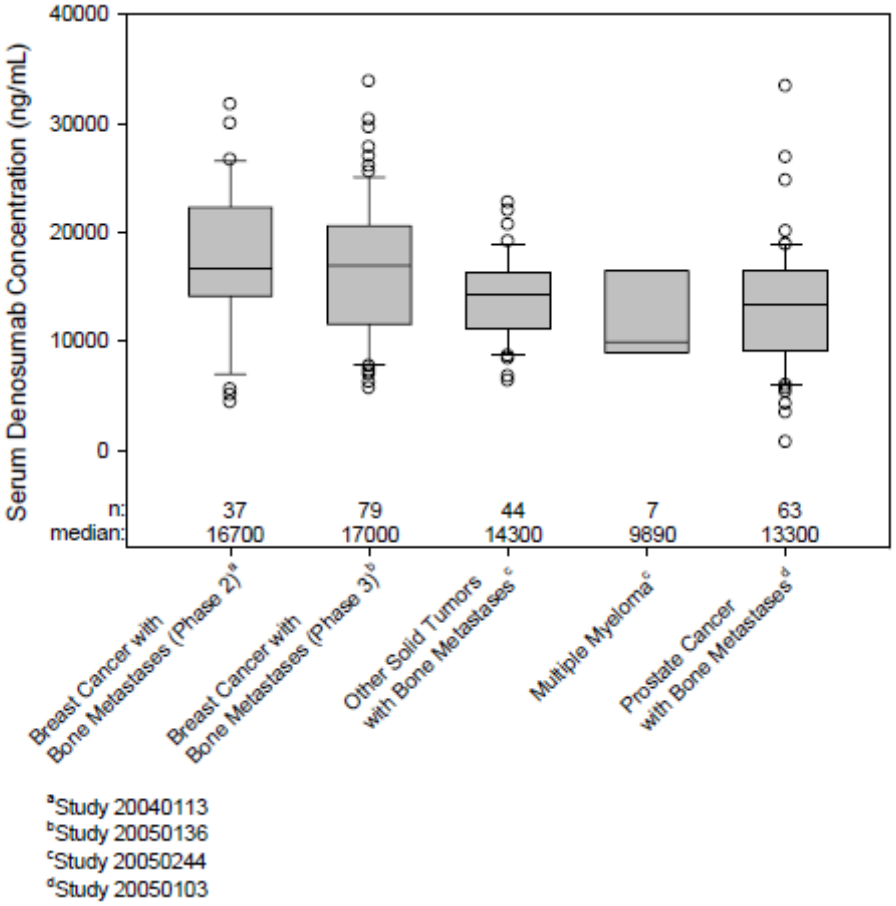
Figure 2. Trough Denosumab Concentrations One Month Post 120 mg SC

Note: The MM cohort is small and the apparent decreased trough concentrations are not in keeping with Phase I trial results.



[a]Study 20060446
[b]Study 20040113
[c]Study 20050136
[d]Study 20050244
[e]Study 20050103

Figure 3. Trough Denosumab Concentrations Three Months Post 120 mg SC Fourth weekly



Linear clearance was found to be statistically different in the popPK Study 111914 for several disease states (MM, breast cancer, prostate cancer, giant cell tumour and 'other tumours'). However, the magnitude of the covariate effect was small (ranging from 1.15-1.39; refer to Table 6 above) and of no clinical significance, particularly in context of the unexplained between subject variability and effect of body weight. However, the effect of MM was significant with a factor of 1.71 (95% CI 1.68,1.74).

Special populations

Paediatrics

No paediatric studies have been performed as the sponsor has not sought an indication in this population.

Elderly

No significant effect of age on denosumab PK was noted in non-compartmental studies (Studies 2006-0446 and 2004-0113). The popPK Study 111914 showed a decline in absorption rate with increasing age up to 70 years, after which it remained stable.

Gender

No significant effect of gender on PK was seen in non-compartmental or popPK studies.

Weight

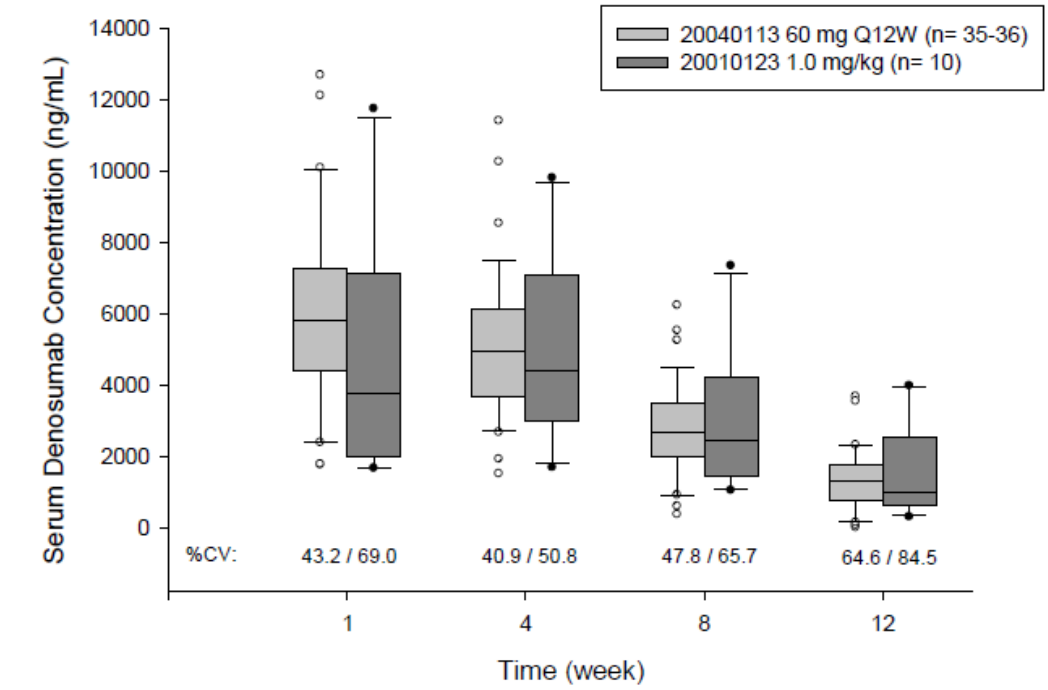
In non-compartmental studies, AUC and C_{max} following a single dose of 120 mg SC declined with both increasing total body weight and body mass index (BMI) in the healthy volunteers and subjects with breast cancer (Study 2004-0113). However, in the context of significant between subject variability, the trend was modest. As is generally the case in popPK studies, body weight was found to be the covariate of greatest significance to PK parameters (principally linear clearance and volume of distribution; Allometric scaled body weight (power 1) was assigned in the structural model for both linear clearance and volume of distribution). Steady-state AUC (with 120 mg fourth weekly dosing) was 48% higher and 46% lower for 45 kg and 120 kg subjects, respectively, compared with the standard 66 kg subject. The significant change in exposure with body weight is demonstrated in Figure 6. The reason that weight does not exist in the summary table of covariates in the population PK study is that it was chosen to be included in the 'base model'. This is not an uncommon practice with some modellers as the strength of association of body weight to clearance and volume of distribution is generally very strong and therefore assumed to exist (and therefore not tested as a potential covariate).

Discussion regarding fixed versus weight-based dosing is relevant at this point. The sponsor has chosen a fixed-based dosing scheme, which offers simplicity of administration. Generally, a weight-based dosing scheme for a drug would be more likely to achieve serum concentrations at the desired target range for a higher proportion of subjects. The sponsor contends that weight-based dosing is not necessary for denosumab as the unexplained population PK variability outweighs the variability seen with weight. It is difficult to account how this might be the case, given the CV of between subject variance of clearance (the key parameter determining exposure for maintenance dosing) was only 34%.

As way of illustrating the assertion, an indirect comparison between a fixed dose (Study 2004-0113) and weight-based dosing (Study 2001-0123) was provided by the sponsor (see Figure 4 for the 60 mg 12-weekly dosing; the 180 mg 12-weekly dosing illustration is similar). This comparison is inconclusive for several reasons. Firstly, the numbers of subjects are small (for example n=10 for the weight-based cohort) and weight variation in these cohorts was not large (ideally for this sort of analysis, randomisation with stratification for weight would be required). Secondly, the population was different, with Study 2001-0113 containing only subjects with breast cancer whereas Study 2001-0123 had seven subjects with breast cancer and three with MM (a difference in clearance was demonstrated for MM subjects in the population pharmacokinetic studies). Finally, a single dose over twelve weeks is compared and not the proposed dosing regimen of fourth weekly cumulative dosing.

Given the high affinity of denosumab for RANKL, the sponsor suggests that a fixed dose of 120 mg will provide comparable decreases in free ligand across a wide range of body weights. This assertion is correct, however, is not unexpected given the dosing regimens chosen and explained further in the PD summaries.

Figure 4. Box Plots for Serum Denosumab Concentrations from Post-hoc Comparison of Study 2004-0113 and Study 2001-0123



Box=interquartile range, line=median, whiskers=10th and 90th percentiles, dots=outliers

Race

A predominance of Caucasian subjects in the PK trials precluded comparisons in non-compartmental analyses. In the popPK Study 111914, subjects with Black and Hispanic ethnicity had 21% to 24% higher linear clearance than Caucasian patients.

Renal and hepatic impairment

Given denosumab is not cleared via renal or hepatic mechanisms it is unlikely that renal or hepatic impairment would be relevant to its PK. This was confirmed for adult subjects with chronic renal impairment in Study 2004-0245 (evaluated by TGA previously). No specific hepatic impairment studies have been performed.

Evaluator's overall comments on pharmacokinetics in special populations

The variability demonstrated is generally small in each of the various special populations, particularly in relation to the unexplained between subject variability. Therefore, it is unlikely that this observed variability in special populations has significant clinical relevance.

Interactions

No formal human biomaterial *in vitro* or *in vivo* drug drug interaction studies have been performed by the sponsor. Indirect comparisons between Phase II and III trials provide supportive data for prior bisphosphonate and concurrent chemotherapy use.

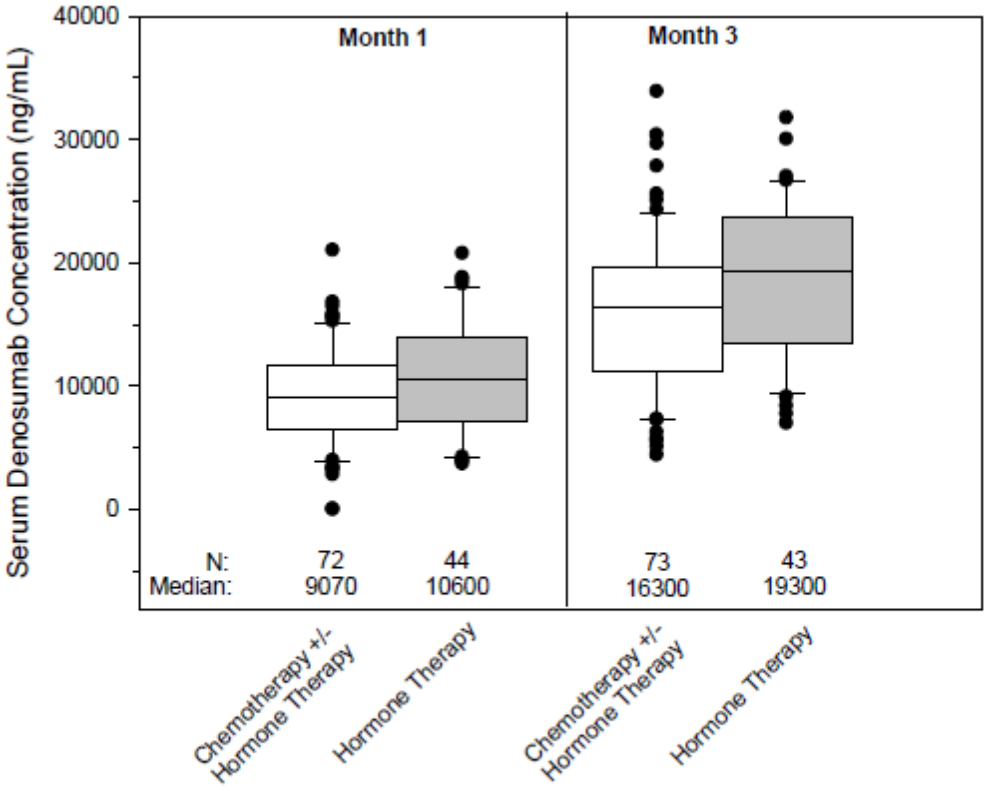
The sponsor justifies the absence of formal interaction studies based on the primarily on the non-hepatic mechanism of elimination for denosumab. Additionally, while some cytokines (biochemically, denosumab is considered a cytokine) can modulate cytochrome P450 enzyme

systems, this is unlikely to occur with denosumab given that RANKL is not constitutionally expressed in the human liver and that no role for RANKL in CYP pathways has been established as yet. Furthermore, data indicates that the RANK receptor is not expressed in the liver. The sponsor concedes that indirect drug interactions could potentially occur but provided further justifications to support their view that this is of low .clinical relevance.

To determine the effect of prior bisphosphonate treatment, the Phase II Study 2004-0113 (subjects with advanced breast cancer with nil prior bisphosphonate use) was compared with the advanced breast cancer subset of the Phase II Study 2004-0114 (subjects with various forms of advanced cancer with at least 2 months of prior bisphosphonate exposure). Due to the absence of a 120 mg dosing group in Study 2004-0114, comparison was made between the 180 mg twelve-weekly dosing groups. No difference in denosumab concentrations was seen at 1 and 3 months post dose.

Similarly, indirect assessment of the effect of type of concurrent therapy (chemotherapy with or without hormonal therapy versus hormonal therapy alone) was assessed in the Phase II Study 2004-0113 and the Phase III Study 2005-0136 (subjects with advanced breast cancer). Randomisation in both these studies was stratified by concurrent chemotherapy and hence both trials were combined to facilitate indirect interaction analysis. Denosumab concentrations at 1 and 3 months post dose (120 mg SC) demonstrated a <19% mean difference between the chemotherapy and hormonal therapy alone groups. Interquartile plots had significant overlap, suggesting that there is likely to be no significant (statistically and clinically) PK interaction effect (see Figure 5).

Figure 5. Serum denosumab concentrations 1 and 3 months post 120 mg SC dose (Studies 2004-0113 and 2005-0136)



Box = interquartile range, line = median, whiskers = 10th and 90th percentiles, dots = outliers

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The popPK Study 111914 did demonstrate a significant effect of concurrent aromatase therapy on linear clearance (magnitude of effect 0.795; 95% CI 0.714, 0.876). This effect was in context of an apparent 15% increase in linear clearance in breast cancer subjects, providing a counter-balancing effect on clearance in this population. Given that the aromatase treated subject data came from a single trial, the apparent effect could also represent a study effect rather than a true drug effect.

Evaluator's overall comments on pharmacokinetic interactions

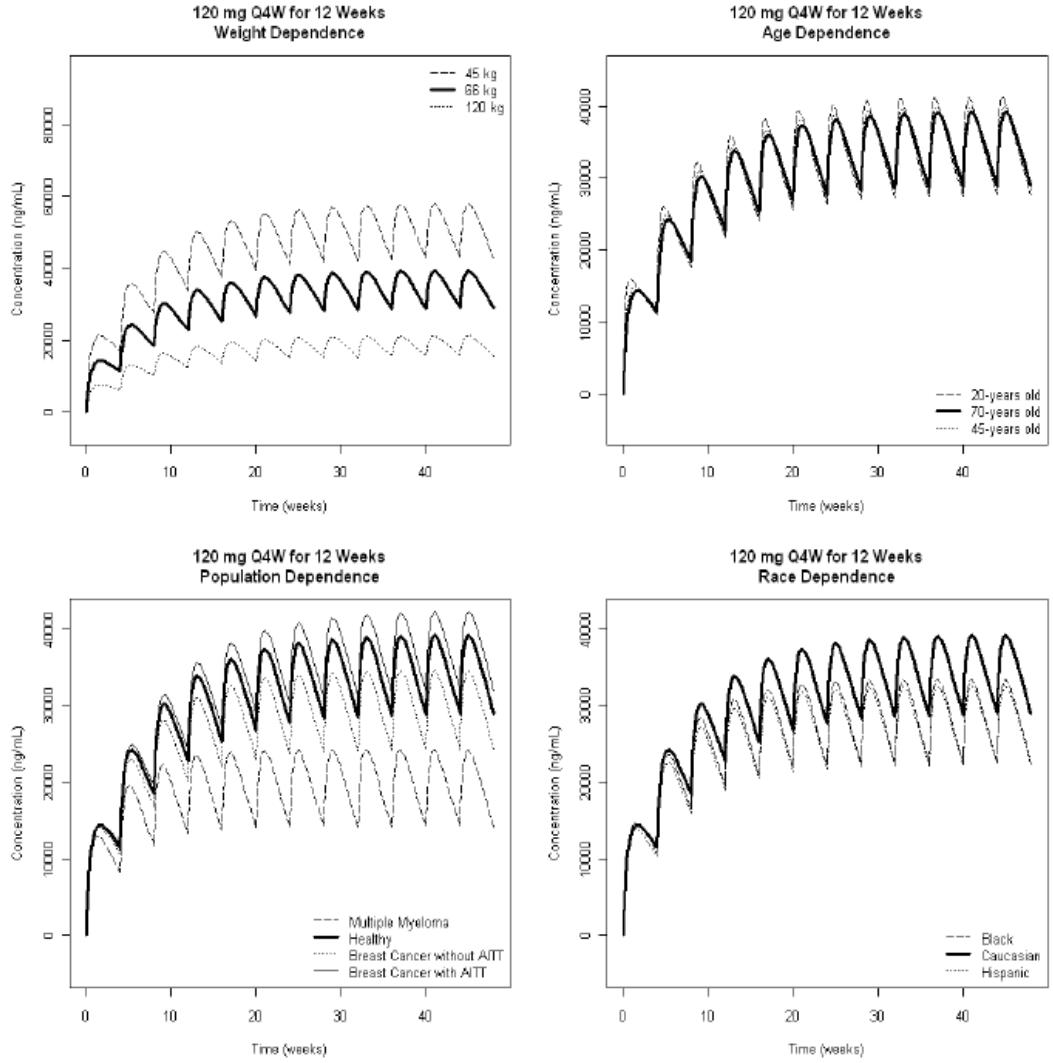
From the limited comparative data available, no clinically significant PK drug drug interactions have been identified. No formal drug interaction studies have been provided. The sponsor's justification is noted. Based on the properties of denosumab it would be unlikely that significant PK drug interactions existed.

Exposure relevant for safety evaluation

At near steady-state (post dose 5) at the proposed dosing (120 mg SC fourth weekly), the mean C_{max} is 2280 ng/mL (SD 14800 ng/mL) and the mean AUC is 723000 ng.day/mL (SD 684000) in subjects with advanced breast cancer with metastasis (Study 2004-0113).

Representative exposure curves from population modelling are provided in Figure 6 (popPK Study 111914).

Figure 6. Population-modelled Denosumab Exposure with 120 mg Fourth weekly Dosing



Evaluator's overall conclusions on pharmacokinetics

The pharmacokinetics of denosumab is well described by a two compartmental model with parallel non-linear and linear elimination pathways. This model is in keeping with the likely physiological distribution and clearance pathways.

The key pharmacokinetic properties are:

- Dose proportionality in the range of proposed therapeutic dosing. Above, but not below 1mg/kg, approximate dose proportionality is seen.
- Subcutaneous bioavailability of 62% with time to maximal concentration approximately two weeks with fourth weekly maintenance dosing.
- Total volume of distribution approximately 4 L, suggesting that widespread distribution outside of the vascular compartment does not occur.
- Steady state achieved after six doses (fourth weekly dosing).

- Mean beta-phase half life ranging from 25-35 days, with elimination likely occurring through the endogenous immunoglobulin clearance pathways.
- Significant inter individual variability in the pharmacokinetics.
- Higher clearance seen in the multiple myeloma subjects (by factor of 1.71), the reason for which is unclear. No clinically significant difference in pharmacokinetics exists between other solid tumour types.
- Significant variance of exposure with body weight, but not age, race, gender or renal function

The sponsor proposes a fixed dose rather than weight-base dosing regimen. The rationale for this is explained above but it would seem difficult to justify this on PK parameters alone.

Pharmacodynamics

Introduction

Pharmacodynamic (PD) information is gathered from four Phase I studies in healthy subjects (evaluated by TGA previously), a single Phase I study in patients with chronic renal impairment (evaluated by TGA previously), two Phase I studies in subjects with advanced cancer (2001-0123 and 2004-0176; already outlined in the PK section), four Phase II studies (two of which are primary PD studies and two are efficacy/safety studies for other indications) and one population PK/PD analysis. Basic characteristics of all studies are outlined in Table 5.

Outline of Primary PD Phase II Trials

Study 2004-0113 was a multicentre, randomised, multiple dose, parallel-group study in subjects with advanced breast cancer and bone metastasis and no previous exposure to bisphosphonates (n=255). Subjects were randomised (n~40 per group and stratified to concurrent treatment) to denosumab 30, 120 or 180 mg SC fourth weekly; denosumab 60 or 180 mg twelfth weekly; or IV bisphosphonate fourth weekly. Treatment continued for 25 weeks with follow-up visits at Weeks 33, 45 and 57. The primary outcome was the percentage change from baseline in urinary NTX[16]/creatinine (Cr) at Week 13.

Study 2004-0114 was a multicentre, randomised, parallel-group, multi-dose study in subjects with advanced solid tumour cancer (excluding lung cancer) or MM with bone involvement (n=111). Subjects were required to have received at least 8 weeks of IV bisphosphonate and have an uNTX/Cr level > 50 nM/mM prior to enrolment. Subjects were randomised (stratified by cancer type) to receive denosumab 180 mg SC twelfth weekly, denosumab 180 mg SC fourth weekly or continued on IV bisphosphonate. Treatment continued for 25 weeks followed by an optional 105 week extension phase. All subjects were followed to 32 weeks. The primary outcome was the proportion of subjects with uNTX/Cr < 50 nM/mM.

Primary pharmacology

Bone resorption as measured by urine NTX (corrected to urine creatinine) was the primary surrogate endpoint used in the PD studies. Clinical studies suggest that uNTX correlates with the presence and progression of bone metastasis and skeletal complications in the setting of advanced cancer and multiple myeloma. It was also previously used to support registration of other agents (zoledronic acid) for similar indications as proposed.

Further evidence for the utility of this biomarker as a surrogate measure of SRE comes from data suggesting that the absolute level of uNTX/Cr predicts outcomes in subjects with cancer. For example, one study suggested that subjects with a baseline uNTX/Cr > 100 nM/mM are more likely to experience an SRE or death in the first 3 months of IV bisphosphonate

[16] Urinary collagen Type 1 cross-linked N-telopeptide.

treatment[17]. Moreover, post hoc analysis of several Phase III zoledronic acid trials suggest a 2 fold or greater risk of SRE, disease progression and death in subjects with uNTX/Cr levels>50 nM/mM (both baseline and on treatment).[18,19]

The sponsor suggests that in patients with advanced cancer involving bone and elevated uNTX levels, normalisation of this parameter may have clinical benefit in reducing risk of SRE. However, caution is advised in over interpreting these findings as these trials are observational and may not be relevant to intervention studies. Attempts to treat subjects to an arbitrary targeted uNTX/Cr may not necessarily improve outcomes and would need to be tested in a prospective clinical trial. In contrast to the studies mentioned above[20], showed a correlation between uNTX levels and mortality but could not demonstrate a correlation between uNTX and SRE. The study involved patients with hormone-refractory prostate cancer receiving zoledronic acid that was followed prospectively. Interestingly, the patients recruited into this trial were enrolled out of one centre's screening for the Phase II Study 2004-0114.

The choice of uNTX/Cr as the primary surrogate measure of SRE for clinical trial development would seem appropriate. Serum NTX, bone-specific alkaline phosphatase (BSAP, a marker of bone formation) and serum CTX1 (an alternative bone resorption marker) were also included in some of the PD studies. While these measures are well established in osteoporosis research, their utility in cancer research is significantly less established than uNTX as valid biomarker of response.

Primary PD from Phase I Studies

Study 2001-0123 (single dose denosumab in subjects with breast cancer or MM which was outlined in the PK section) demonstrated a rapid decrease in uNTX/Cr with decline evident on Day 1 (the first sample time-point). A dose-response effect was seen for doses <1 mg/kg with maximum median uNTX/Cr suppression increasing from 35% to 78% in subjects with breast cancer and 35% to 78% in subjects with MM. No apparent dose response was seen at doses >1 mg/kg as demonstrated by maximum median uNTX/Cr suppression at 3 mg/kg of 76% and 52% for the two disease subsets, respectively. In fact, the small MM patient subset had a paradoxical decreased effect at 3 mg/kg compared to all doses above 0.1 mg/kg. The duration of the effect in the breast cancer subset continued through to Week12 (the close of the study) at all doses except 0.1 mg/kg. Results are illustrated in Figures 7 and 8.

Similar trends to uNTX were seen with serum NTX. Declines in BSAP were observed for all doses except 0.1 mg/kg in breast cancer subjects and at 1 and 3 mg/kg in subjects with MM.

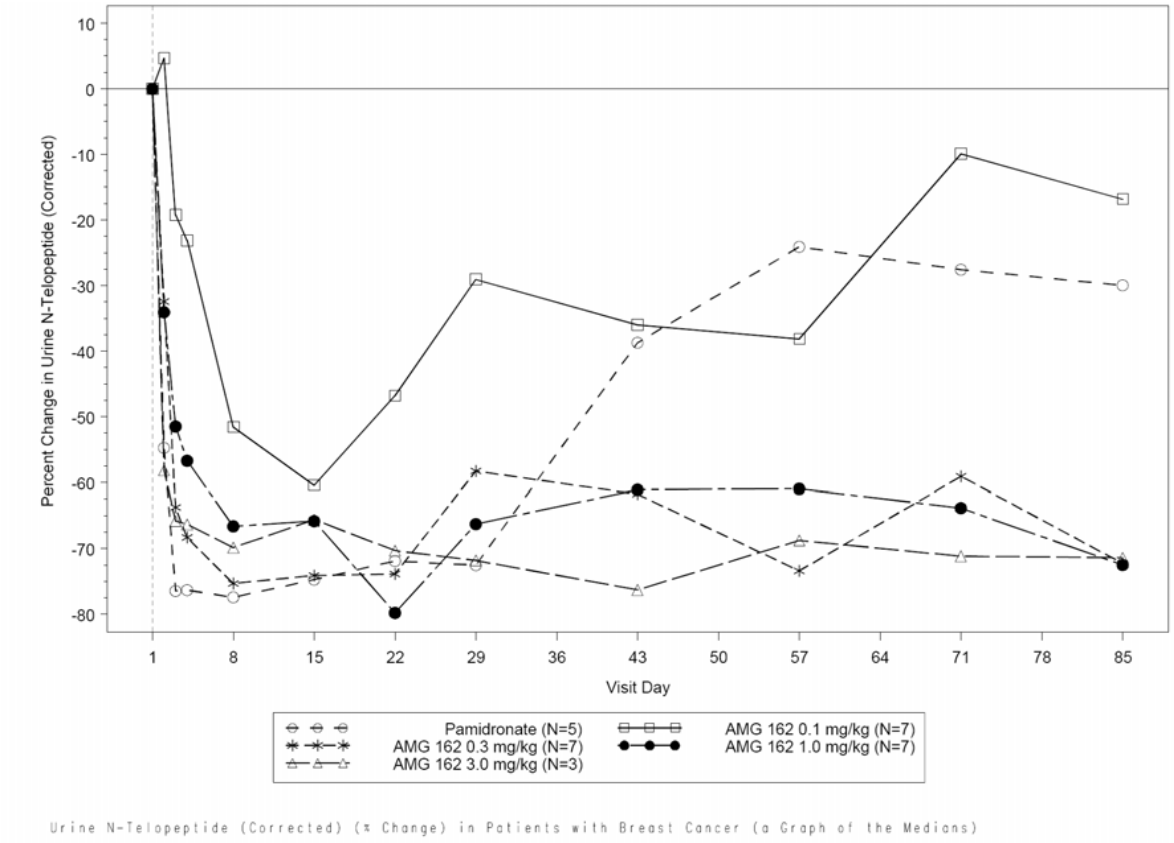
[17] Brown JE, Thomson CS, Ellis SP *et al*. Bone resorption predicts for skeletal complications in metastatic bone disease. *Br J Cancer* 2003; 89: 2031-7.

[18] Brown JE, Cook RJ, Major P. *et al.* Bone turnover markers as predictors of skeletal complications in prostate cancer, lung cancer and other solid tumours. *J Natal Cancer Inst* 2005; 97: 59-69.

[19] Coleman RE, Guise TA, Lipton A. *et al*. Advancing treatment for metastatic bone cancer: consensus recommendations from the second Cambridge conference. *Clint Cancer Res* 2008; 14: 6387-95.

[20] Rajpar S, Massard C, Laplanche A. *et al*. Urinary N-telopetide (uNTx) in an independent prognostic factor for overall survival in patients with bone metastases from castration-resistant prostate cancer. *Ann Oncol* 2010; 21: 1864-9.

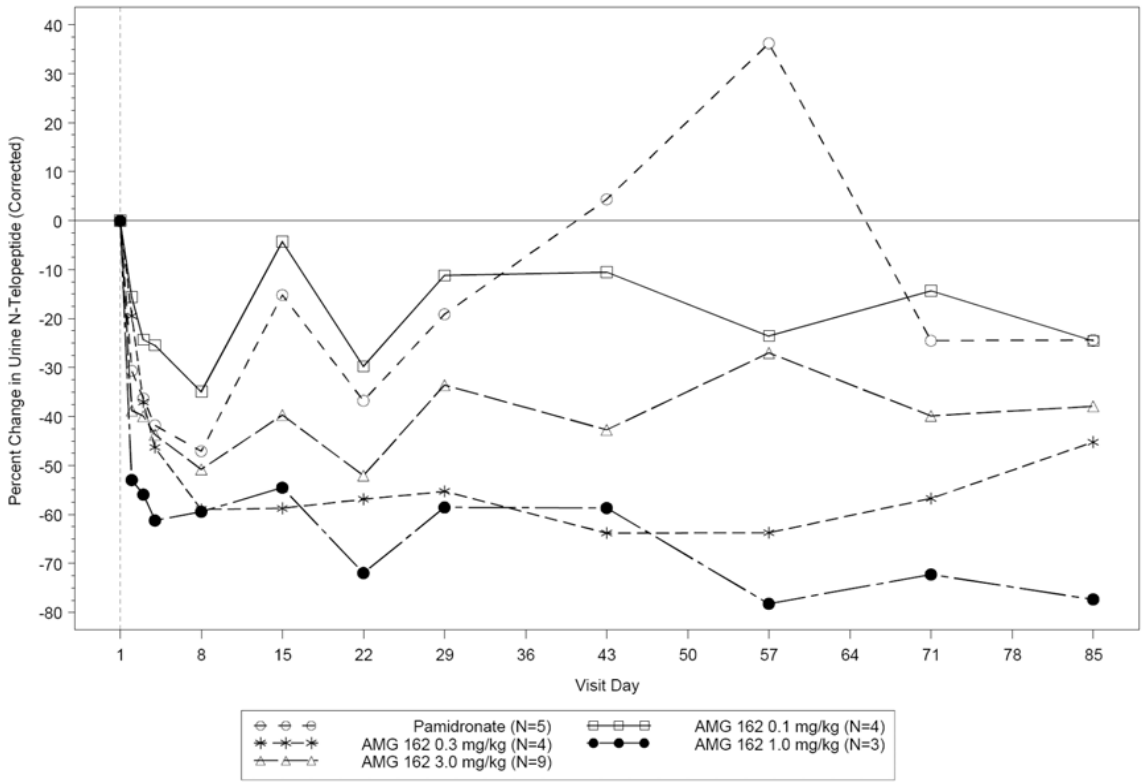
Figure 7. Median Percentage Change in uNTX/Cr over Time in Subjects with Breast Cancer (Study 2001-0123).



Urine N-Telopeptide (Corrected) (% Change) in Patients with Breast Cancer (a Graph of the Medians)
Program: /stat/opg/20010123/analysis/final/graphs/g_ntxrat_pch_median.sas
Output: median_pch_NTX_URINE_CR_bc.cgm (Date Generated: 17DEC2004) Source: btm.sas7bdat

Note: The subject number (n) = N, with the following exceptions: At various timepoints from day 4 to 71, n = 6 or 5 in the 0.1 and 1-mg dose cohorts and n = 6 in the 0.3-mg dose cohort. At day 85, n = 6 for all 3 of these cohorts.

Figure 8. Median Percentage Change in uNTX/Cr over Time in Subjects with MM (Study 2001-0123)

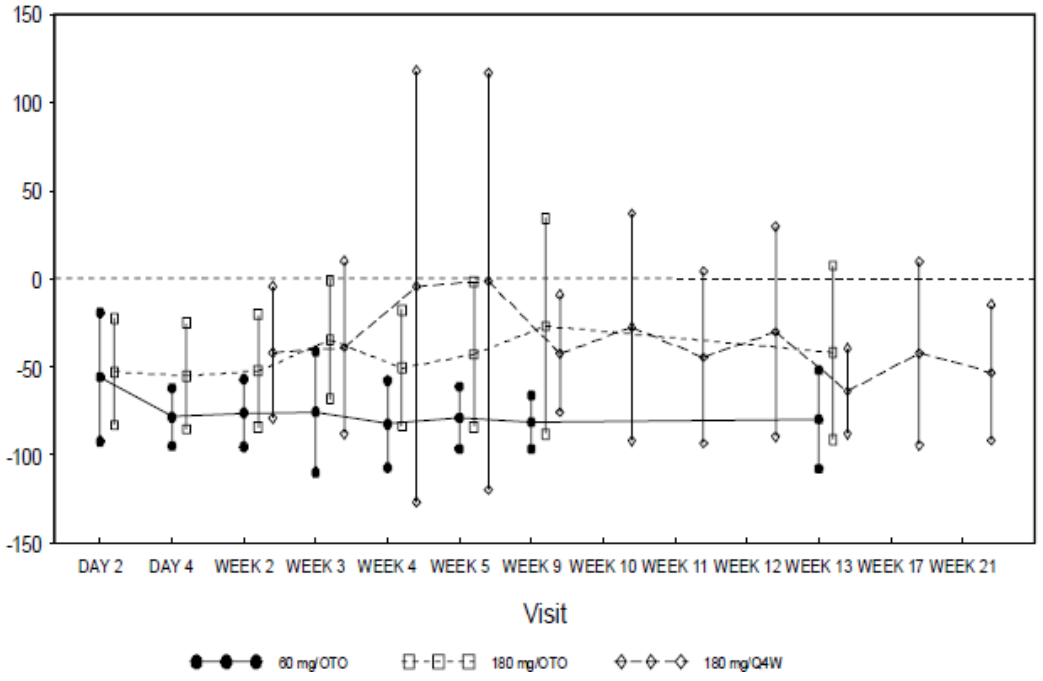


Urine N-Telopeptide (Corrected) (% Change) in Patients with Multiple Myeloma (a Graph of the Medians)
Program: /stat/opg/20010123/analysis/final/graphs/g_ntxrat_pch_median.sas
Output: median_pch_NTX_URINE_CR_mm.cgm (Date Generated: 17DEC2004) Source: btm.sas7bdat

Note: The subject number (n) = N, with the following exceptions: In the 0.1-mg/kg dose cohort, n = 3 from day 43 to 85. In the 3-mg/kg dose cohort, n = 8 on day 15. In the pamidronate group, n = 4 from day 29 to 57, and n = 3 on days 71 and 85.

Study 2004-0176. This study involved Japanese subjects with breast cancer and associated bone metastases and the details of the study were outlined in the section on PK above. This study demonstrated a decline in uNTX/Cr from the first sampled time-point. A lack of dose-response was seen at the doses tested (single doses of 60 and 180 mg SC; and 180 mg given every 4 weeks). A greater mean extent and duration of suppression was seen with the single 60 mg cohort compared to the 180 mg cohort. The sponsor suggests this observation may have related to a greater baseline uNTX/Cr in this cohort (108 versus 44 nmol/mmol). Median percentage decrease in uNTX/Cr was 92% and 61% at 13 weeks for the 60 and 180 mg cohorts, respectively. In the 180 mg fourth weekly dose cohort, greater suppression was seen after the third dose than after the first and second doses (median suppression 36%, 44% and 60% at Weeks 5, 9 and 13, respectively). However, percentage suppression after 12 weeks did not differ between the 180 mg single dose (61%) and 180 mg fourth weekly dose (60%). Mean change in uNTX/Cr is demonstrated in Figure 9.

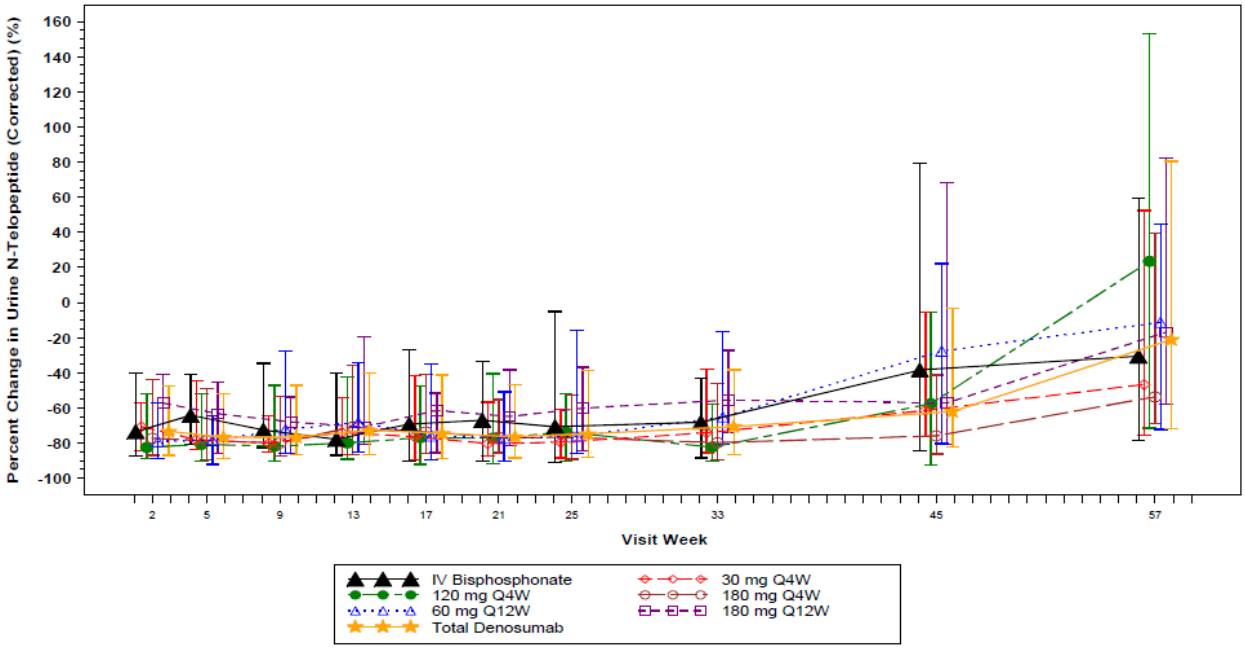
Figure 9. Mean (±SD) Percentage Change from Baseline in uNTX/Cr over Time in Japanese Subjects with Advanced Breast Cancer and Bone Metastasis.



Primary PD from Phase II Studies

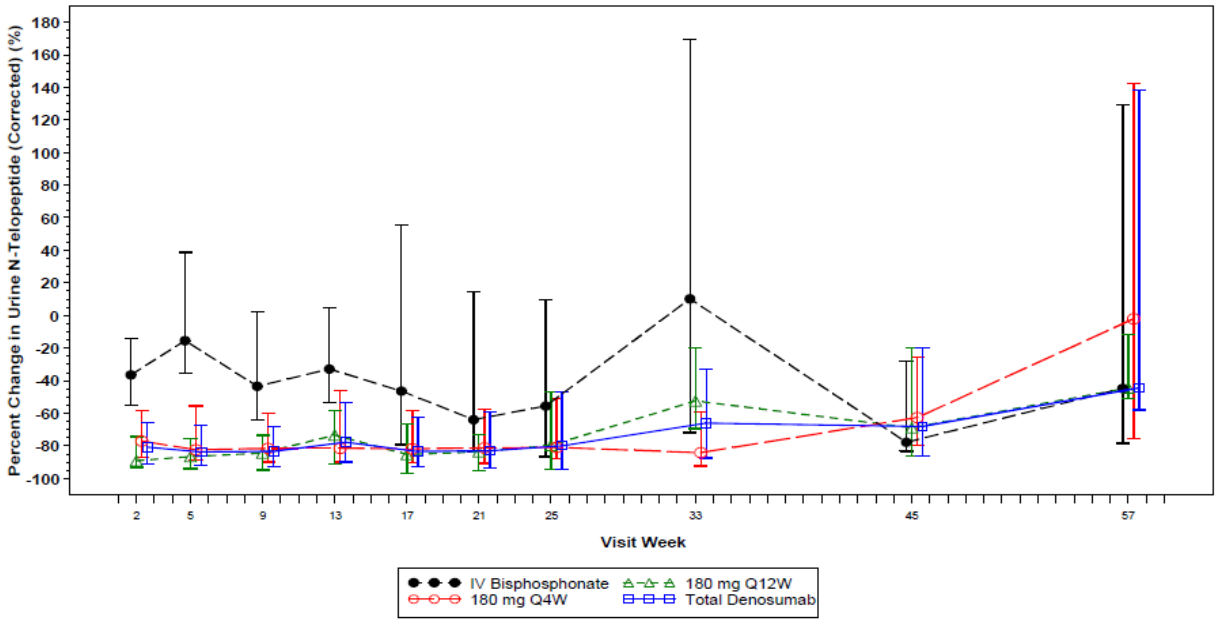
Study 2004-0113. Subjects with breast cancer and bone metastasis not previously exposed to bisphosphonates and administered multiple doses and regimens were enrolled in this study. The results showed a similar degree of uNTX/Cr suppression at Week 13 and 25 by denosumab (all dose groups combined) compared with IV bisphosphonate. A lack of dose response (see Figure 10) was seen between the denosumab groups, with the 30 and 120 mg SC fourth weekly dosing groups having the greatest degree of suppression (median uNTX/Cr suppression at Week 13, 74% and 80%, respectively). Loss of efficacy was seen in the post treatment phase (treatment ceased at Week 25 and subjects were permitted to receive IV bisphosphonate) with the greatest rise in uNTX/Cr seen at Weeks 45 and 57. No difference in the percent change in uNTX/Cr at Week 57 was seen between the IV bisphosphonate group and the combined denosumab groups.

Figure 10. Median (Q1, Q3) Percentage Change in uNTX/Cr from Baseline by Treatment Group (Study 2004-0113).



Study 2004-0114. Subjects with advanced cancer or MM with bone involvement and prior bisphosphonate exposure were enrolled in this study. The results showed a significantly greater ($p<0.001$) proportion of subjects with uNTX/Cr < 50 nM/mM at Week 13 in the combined denosumab treatment arms (71%) compared with the IV bisphosphonate arm (pamidronate or zoledronic acid; 29%). Time to uNTX/Cr < 50 nM/mM was also significantly shorter in the former group (9 days for the combined denosumab group versus 65 days for IV bisphosphonate; $p<0.001$). A lack of dose response between denosumab treatment groups (120 mg fourth weekly dosing and 120 mg twelfth weekly dosing) was observed again (Figure 11).

Figure 11. Median (Q1, Q3) Percentage Change in uNTX/Cr From Baseline by Treatment Group (Study 2004-0114).



Subjects were not on active dose after week 21.
Treatment phase is defined as treatment phase treatment period (first 25 weeks) plus treatment phase follow up (from week 25 to week 57).

Primary PD from Phase III Studies

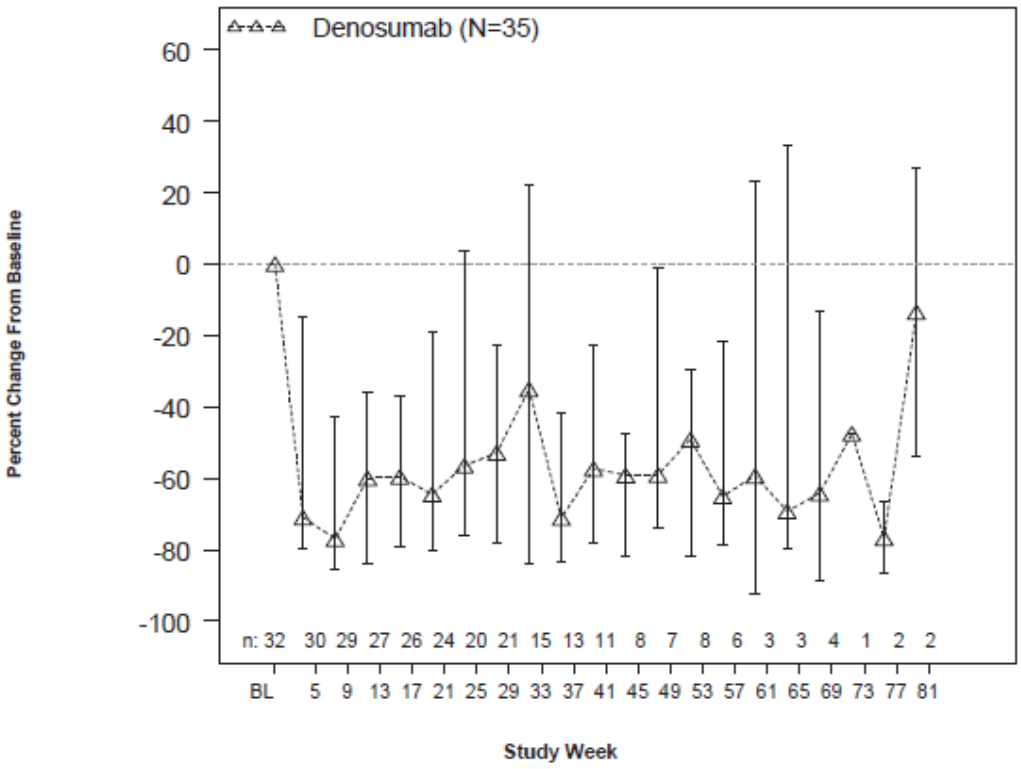
Studies 2005-0136 (breast cancer with bone metastasis), *2005-0244* (advanced non-breast/prostate cancer; and MM with bone involvement) and *2005-0103* (hormone-refractory prostate cancer with bone metastasis) compared denosumab 120 mg SC fourth weekly with zoledronic acid IV 4 mg fourth weekly. Primary endpoints involved efficacy and safety data outcomes but limited PK/PD sampling was also performed. All of these studies demonstrated greater uNTX/Cr suppression at Week 13 in denosumab treated subjects compared to subjects who received IV zoledronic acid. The median percentage change for denosumab treated patients in the Phase III studies was similar to that seen in the earlier Phase II denosumab trials. Suppression of BSAP was also demonstrated at a magnitude similar to the results of the Phase I *Study 2001-0123*.

Preliminary PD from Additional Studies

Preliminary analysis from two further studies for indications different to this submission (Study 2004-0215 [a Phase II trial for treatment of giant cell tumour of bone] and 2005-0134 [a Phase II study of relapsed or plateau-phase MM]) also provided additional yet limited PK/PD data.

Both of these studies utilised a treatment regimen of denosumab 120 mg SC fourth weekly with additional loading dosing on the first dose cycle (Days 8 and 15). Study 2004-0215 evaluated uNTX/Cr, CTX1, BSAP, osteocalcin and TRAP 5b. Study 2005-0134 evaluated CTX1 and BSAP. Results from both studies were similar to the other studies in subjects with malignancy. Results for uNTX/Cr in Study 2004-0215 are provided in Figure 12.

Figure 12. uNTX/Cr Percentage Change from Baseline (Median and Q1/Q3). Preliminary analysis Study 2004-0215



N = Number of subjects who (1) are on study for >= 28 days after the first dose of denosumab; and (2) have at least one baseline tissue and at least one post-dose tissue between week 5 and week 25, or have at least one baseline radiograph and at least one post-dose radiograph between week 5 and week 25.

Program: /stat/amg162/therapeutic/20040215/analysis/final/graphs/program/g_labsum.sas
Output: g14-06_004_001_untx_pchg_eff.cgm (Date Generated: 29JAN2009:15:59:31)
Source Data: adam.albbnsp, adam.aslinf

Secondary pharmacology

Immunogenicity

Immunogenicity studies evaluating the effect of neutralising antibodies on PD were performed in 3508 denosumab-treated subjects. The overall incidence of binding antibodies was 0.4%, most of which were discovered as a transient event. No neutralising antibodies were discovered. Table 7 describes the PK/PD parameters at the time of the positive antibody discovery. No parameter fell outside of the expected range.

Table 7. Serum Denosumab Concentrations and uNTX/Cr for Antibody-positive Subjects

Study	Time of Positive Ab Result (week)	Denosumab Serum Concentration (ng/mL)[a]	Denosumab Serum Concentration Range[b] (ng/mL)	uNTX/Cr Concentration (nmol/mmol)	uNTX/Cr Concentration Range (nmol/mmol)
20040113	57	267	BLQ - 3080	6.89	4.21 - 417
20040113	33	1480	4.12 - 26100	11.6	3.63 - 146
20040113	45	7040	1.76 - 7960	NA	NA
20040114	13	31000	12900 - 50900	47.1	4.94 - 54.4
20040114	1,33	4900	1980 - 22300	177	4.13 - 177
20050134	1	7440	2870 - 25800	NA	NA
20050136	49	NA	NA	6.46	2.20 - 289
20050244	1	NA	NA	4.95	1.74 - 421
20050103	49	NA	NA	5.20	2 - 365
20050103	25	NA	NA	31.5	2 - 365

Ab = antibody; BLQ = below the limit of quantification; uNTX/Cr = urinary N-telopeptide corrected by creatinine (percent change from baseline at month 12); NA = not available

[a] Serum concentration values are presented to 3 significant figures

[b] For antibody-negative subjects

[c] Serum denosumab concentration and uNTx/Cr for individual values and ranges at week 33 (nearest to timing of positive antibody result)

[d] Urinary NTX/Cr individual values and ranges at week 13 (only one uNTx/Cr sample timepoint evaluated during study)

[e] Subjects not randomized to PK substudy, therefore no PK data available

Serum Calcium

Because denosumab acts by inhibiting bone resorption it would be anticipated to have an effect on calcium regulation. Subjects involved in the Phase II and III trials were routinely prescribed calcium and vitamin D supplementation consistent with current standards of care. Transient and generally minor (median decrease < 5%) changes to serum calcium were observed in the studies. Significant hypocalcaemia events did occur in some subjects and are discussed below in the *Safety* section of this AusPAR.

The relationship between serum calcium and denosumab exposure (C_{max} and AUC) was evaluated in Study 2004-0123 (subjects did not routinely receive calcium and Vitamin D supplementation in this study), Study 2004-0113 (patients did receive supplementation) and Study 2004-0245 (in subjects with renal dysfunction). The first two studies are described in the PK section above.

No correlation between C_{max} or AUC and changes in median serum calcium was noted in these analyses. This is not an unexpected finding given the lack of dose response on bone resorptive markers at the doses used in these studies.

Osteoprotegerin (OPG)

Osteoprotegerin (OPG) is the endogenous RANKL inhibitor. The effect of denosumab, compared with IV bisphosphonates, on the serum levels of OPG was evaluated in Studies 2004-0113 and 2004-0114 (both described above). No significant effect was seen.

Relationship between plasma concentration and effect

A pop PK/PD (112014) analysis was performed to explore the correlation between drug concentration and effect. Included were two Phase I studies (2001-0123 and 2004-0176), one Phase II trial (2004-0113) and two Phase III studies (2005-0136 and 2005-0244). A total of 331 subjects with advanced malignancy (breast, other solid tumours or MM) were included. Dose ranges included in the analysis were 0.1-3 mg/kg or 60 to180 mg for fixed dose studies for single dose subjects (n=49) and 30 mg to 180 mg fourth or twelfth weekly (up to 12 months) for multiple dose subjects (n=282). No subject had received prior bisphosphonate therapy. The mean age was 58 years (range 27-82) and the mean body weight was 69 kg (range 40 to 127 kg). Only 12.1% (40) of subjects were male. Sixty-seven percent of subjects were White.

A total of 2122 uNTx/Cr data points were available with seven excluded as outliers. There were 809 data points below the lower limit of quantification (BLLQ) and these were managed with the Beal M3 technique.

An inhibitory sigmoid maximum percent inhibition achievable (I_{max}) model was found to best fit the PD data. Covariates evaluated included age, sex, race, weight and cancer type. Covariates were chosen for inclusion by visual inspection of diagnostic plots followed by a forward inclusion and backward elimination process. No significant effect of any of the tested covariates was found at the doses included in the analysis.

The median uNTx/Cr at baseline was 46.7 nM/mM with a between subject variability (BSV) of 77%. Breast cancer/Other solid tumour subjects had a typical I_{max} (maximum percent inhibition achievable with denosumab) value of 93%, with a typical IC_{50} (concentration of denosumab at which 50% of maximal efficacy is achieved) of 41.2 ng/mL. The between subject variability was 25% for I_{max} and 244% for IC_{50}. Results for MM are included in Table 8. I_{max} was significantly lower for patients with MM (typically 70.7%) suggesting a reduced efficacy of denosumab in suppressing uNTX/Cr in this population.

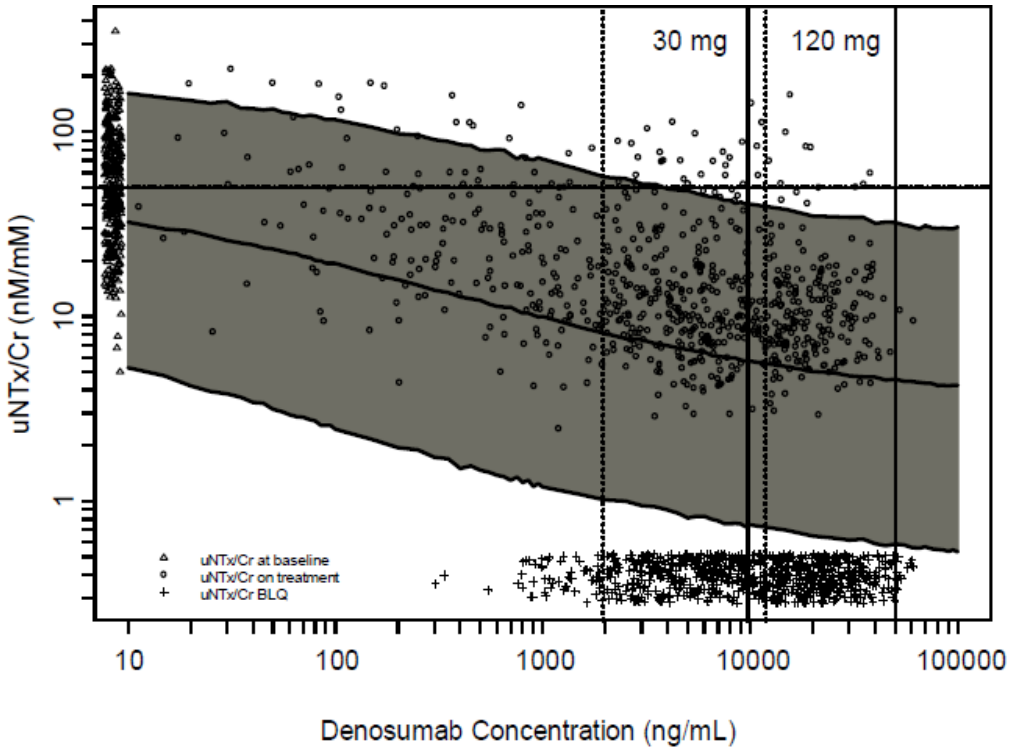
Table 8. Parameter Estimates (Bootstrapped 95% CI) of Population PK/PD Model

	Central Tendency		
Model Parameter	Breast Cancer and Other Solid Tumors	Multiple Myeloma	Between-subject Variability (%)
I_{Max} (%)	93.0 (91.5 – 93.0)	70.7 (55.2 – 77.3)	24.5 (17.7 – 33.5)
IC_{50} (ng/mL)	41.2 (33.9 – 112)	53.1 (29.4 – 259)	244 (213 – 312)
λ	0.676 (0.581 – 1.02)		--

Correlation (r2) between I_{Max} and IC_{50}: 0.131 (95%CI: 0.0388 – 0.273)
Residual error (%): 49.2 (95%CI: 44.2 – 55.3)

Figure 13 demonstrates the observed compared with the predicted concentration effect relationship. A line has been drawn at uNTX/Cr 50 nM/mM (the upper limit of the normal range for young people) consistent with the previous post hoc analysis, suggesting a 2 fold increased risk of SRE in subjects treated with zoledronic acid at this level. However, as mentioned previously, there is no prospective intervention data suggesting that targeting a specific uNTX/Cr level improves efficacy outcomes. The sponsor points out that serum denosumab concentrations at steady state with 120 mg fourth weekly dosing in this population is associated with 95% of subjects achieving uNTX/Cr < 50 nM/mM during the entire dosing interval. However, the proportion of subjects achieving this target uNTX/Cr at 30 mg also appears favourable (around 90%).

Figure 13. Observed and Predicted (90% Predicted) Relationship Between uNTX/Cr and Serum Denosumab Concentrations (popPK/PD analysis 112014)



Pharmacodynamic interactions with other medicinal products or substances

Indirect comparative analyses of the effect of prior IV bisphosphonates and concurrent chemotherapy were described in the PK interaction section. In both these analyses, no significant effect was seen on the primary PD parameter uNTX/Cr.

Clinical evaluator's overall conclusions on Pharmacodynamics

The following is a summary of the pharmacodynamic properties of denosumab, as identified in the Phase I, II and III studies, in advanced cancer:

- Rapid and sustained decrease in the primary pharmacodynamic biomarker urinary NTX normalised for creatinine (uNTX/Cr).
- Generally, a dose response relationship was seen for doses below but not above 1 mg/kg in any trial during the clinical development program. In fixed rather than weight based trials, a minimal dose response effect was seen with doses greater than 30 mg.
- A 75%-90% reduction in uNTX/Cr was seen for doses greater than 1 mg/kg. The duration of the effect on uNTX/Cr continued at least until Week 12 at all doses greater than 0.1 mg/kg. The suppression of uNTX/Cr was equivalent or greater than IV bisphosphonate in comparative studies.
- Generally transient and minor decreases in serum calcium levels were noted with denosumab administration. There was no apparent dose response effect on serum calcium levels (in keeping with the lack of dose response on bone turnover markers).
- Population PK/PD analysis found the IC_{50} to be 41.2ng/mL in the solid tumour group with a between subject variability of 244%. I_{max} was 93% in the solid tumour group, with a between subject variability of 24.5%. A lower I_{max} was seen in the multiple myeloma group (70.7%) suggestive of a reduced efficacy in this population.

- On population PK/PD analysis, an apparent dose response is seen but the clinical relevance of the improvement in uNTX/Cr suppression from 30 mg to 120 mg would seem doubtful.

The lack of dose response at doses greater than 1 mg/kg is in keeping with the pharmacokinetic modelling that suggested greater than 97.5% receptor saturation for all subjects (including the high-weight, high-clearance subjects) at the proposed dose of 120 mg fourth weekly. This correlates to 99.5% free RANKL reduction from baseline in the modelling. This suggests that the chosen dose range provides serum concentrations within or above the bounds of the EC_{100} (the concentration that achieves 100% of the maximum possible efficacy). This is a departure from the traditional concept of drug dosing and from the EMA guideline adopted by the TGA[21], where the selected dose range normally falls on the 'steep part of the dosing curve' (that is, around the EC_{50}). The lack of dose response seen also explains the lack of difference on pharmacodynamics with weight based dosing compared with fixed dosing at the proposed dosing range. If a lower dosing schedule were selected, a pharmacodynamic benefit of weight based dosing may have been seen.

This dose selection strategy is not uncommon with monoclonal antibodies, with modelling from many PK/PD studies suggesting 100% receptor saturation with these agents. Nor is this strategy always inappropriate. For example with medicines with a low toxicity (and a high 'therapeutic window') dosing at or above the E_{max} (or I_{max} in this case) can be a useful means of increasing the duration of the biological effect and thus the dosing interval. However, dosing at this level does not improve the efficacy of the agent and can potentially increase adverse events.

The sponsor's rationale for their dose selection (120 mg fourth weekly) is based primarily on the population PK/PD analysis:

- It results in a higher proportion of subjects with uNTX/Cr levels < 50nM/mM relative to 30 mg fourth weekly dosing.
- It results in higher proportion of subjects with uNTx/Cr suppression > 90% compared with twelfth weekly dosing.
- 120 mg is the lowest fourth weekly dose resulting in the maximal proportion of subjects with uNTx/Cr suppression > 90%.
- It results in substantial reduction in the absolute variability in uNTx/Cr as compared with baseline.

The rationale essentially confirms a chosen dose that achieves I_{max} in all participants with a single dosing strategy. While an explanation of the dosing rationale is welcome, criticism could be made in regard to clinical relevance of dosing above I_{max}. The minimum dose required to achieve clinically relevant outcomes and the dose related safety profile have not been well established. The effect of increased dosing intervals on relevant outcomes could have also been explored further.

Efficacy

Introduction

The requested indication is broadly defined by the sponsor with no explicit definition of 'skeletal related events' in the proposed indication statement. An SRE is proposed to encompass events such as pathologic fractures; radiation or surgery to bone; or spinal cord compression due to cancer. This definition of SRE was used consistently in all of the pivotal studies. 'Advanced malignancies' was not defined within the sponsor's application but the submitted

[21] ICH Topic E4 . Dose Response Information to Support Drug Registration. CPMP/ICH/378/95. http://www.tga.gov.au/pdf/euguide/ich037895en.pdf

clinical studies including a broad range of malignant conditions in adult subjects, including breast cancer, hormone refractory prostate cancer, multiple myeloma and 'Other solid tumours' (the majority of which being non-small cell lung cancer). The current standard of care for the prevention of malignancy related SRE is intravenous zoledronic acid 4 mg which has been approved for the following (and similar) indication:

> *"Prevention of SREs (pathological fracture, spinal cord compression, radiation to bone or surgery to bone) in patients with advanced malignancies involving bone. Treatment of tumour induced hypercalcaemia."*

A request for an indication in hypercalcaemia of malignancy has not been sought in the current Australian application although time to first SRE or hypercalcaemia of malignancy was examined as an exploratory outcome in the pivotal denosumab studies.

The efficacy evaluation centres on three pivotal studies, each with a non-inferiority comparison to zoledronic acid for the prevention of SREs in different patient populations with cancer. Table 9 provides a tabular summary of the denosumab clinical studies. Study 2005-0136 enrolled 2046 patients with breast cancer (n=1026 randomised to denosumab), Study 2005-0103 recruited 1901 subjects (n=951 randomised to denosumab) with hormone refractory prostate cancer and Study 2005-0244 enrolled 1776 patients (n=889 randomised to denosumab) with either advanced multiple myeloma or various solid tumours other than breast or prostate cancer.

Table 9. Summary of clinical efficacy and safety studies.

Study ID	No. of centres (location)	Design	Study posology	Study objective	Subjects by arm: Entered (Completed.)	Duration of study	Gender: M/F (Age)	Diagnosis & main inclusion criteria	Primary endpoint
Main (pivotal) studies									
2005-0136	322 (Int)	R, DB, AC, P3	D 120mg SC Z 4mg IV Both q4w	Efficacy Safety	D 1026 (468) Z 1023 (461)	34 months from study start	17/2029 (56.7)	Confirmed breast adenocarcinoma with ≥ 1 current or prior bone metastasis. No bisphosphonate exposure	Time to first on study SRE (non-inferiority)
2005-0103	342 (Int)	R, DB, AC, P3	D 120mg SC Z 4mg IV Both q4w	Efficacy Safety	D 951 (228) Z 953 (208)	41 months from study start	1901/0 (70.8)	Confirmed hormone-refractory prostate cancer with≥ 1 current or prior bone metastasis. No bisphosphonate exposure	Time to first on study SRE (non-inferiority)
2005-0244	321 (Int)	R, DB, AC, P3	D 120mg SC Z 4mg IV Both q4w	Efficacy Safety	D 889 (180) Z 890 (178)	34 months from study start	1140/636 (60)	Confirmed advanced cancers including solid tumours (not breast or prostate), MM, lymphoma with ≥ 1 current or prior bone metastasis.	Time to first on study SRE (non-inferiority)

Other Studies									
2005 -136 DBE*	322 (Int)	R, DB, AC, P3	D 120mg SC Z 4mg IV Both q4w	Efficacy Safety	D 1026 (366) Z 1023 (386)	39 months from study start	17/2029 (56.7)	Extended blinded-treatment phase for study 2005-0136	Time to first on study SRE (non-inferiority)
2005 - 0244 DBE*	321 (Int)	R, DB, AC, P3	D 120mg SC Z 4mg IV Both q4w	Efficacy Safety	D 889 (123) Z 890 (128)	40 months from study start	1140/636 (60)	Extended blinded-treatment phase for study 2005-0244	Time to first on study SRE (non-inferiority)
2001 - 0123	8 (US)	R, DB, AC, P1	D 0.1, 0.3, 1, 3mg/kg P 90mg Single dose study	PK, PD Safety	D 44 P 10	16 weeks	14/40 (~60)	Confirmed MM or breast cancer with bone involvement	Incidence of adverse events
2004 - 0176	3 (Japan)	OL, P1	D 60, 180mg single dose 180mg q4w	PK, PD Safety	D 18	12 weeks	0/18 (54.8)	Breast cancer with a least 1 bone metastasis	Incidence of adverse events
2004 - 0113	56 (Int)	R, PB, AC, P2	D 30, 120, 180mg q4w 60, 180mg q12w BP–	PK, PD Efficacy Safety	D 212 BP 43	57 weeks	0/255	Confirmed breast adenocarcinoma with at least 1 bone metastasis, no prior bisphosphonate exposure	Change in uNTX/Cr at week 13

			standard care						
2004-0114	26 (Int)	R, OL, AC, P2	D 180mg q4w or q12w BP – standard care	PK, PD Efficacy Safety	D 74 BP 37	25 weeks (± 105 week extension)	55/56 (62.5)	Confirmed solid tumour carcinomas (except lung) or MM with evidence of 1 or more bone lesions	Proportion of patients with uNTX/Cr < 50nM/mM at week 13
2005-0134	11 (US, Australia)	OL, P2	D 120mg q4w + loading doses day 8 +15	PK, PD Efficacy† Safety	D 96	Planned 6 months exposure	57/39 (62)	Relapsed MM or plateau-phase MM	Proportion of subjects with a complete or partial response
2005-0215	8 (Int)	OL, P2	D 120mg days 1, 8, 15, 29 then q4w	PK, PD Efficacy† Safety	D 37	Ongoing, endpoint determined	17/20 (34)	Confirmed giant cell tumour of bone with recurrent or unresectable disease	Response rate
2005-0147	319 (Int)	R, DB, PC, P3	D 120mg q4w P q4w	Interim Safety only	D ~700 P ~700	Ongoing, endpoint determined	1435/0	Hormone-refractory prostate cancer at high risk of metastasis	Bone-metastasis free survival

D = Denosumab; P = placebo; Z = Zoledronic acid; P=Pamidronate; BP = IV bisphoshonate (Z or P, standard of care for centre);q4w = every four weeks; q12w = every twelve weeks

R = randomised; DB = double blind; PB = partially blinded; PC = placebo controlled; AC = active controlled; OL = open-label

Int = International; US = United States of America

P1 = Phase I; P2 = Phase II, P3 = Phase III

* Further extended open-label phase is ongoing †Efficacy for an alternate indication, hence not discussed here. Interim analysis only available for these studies.

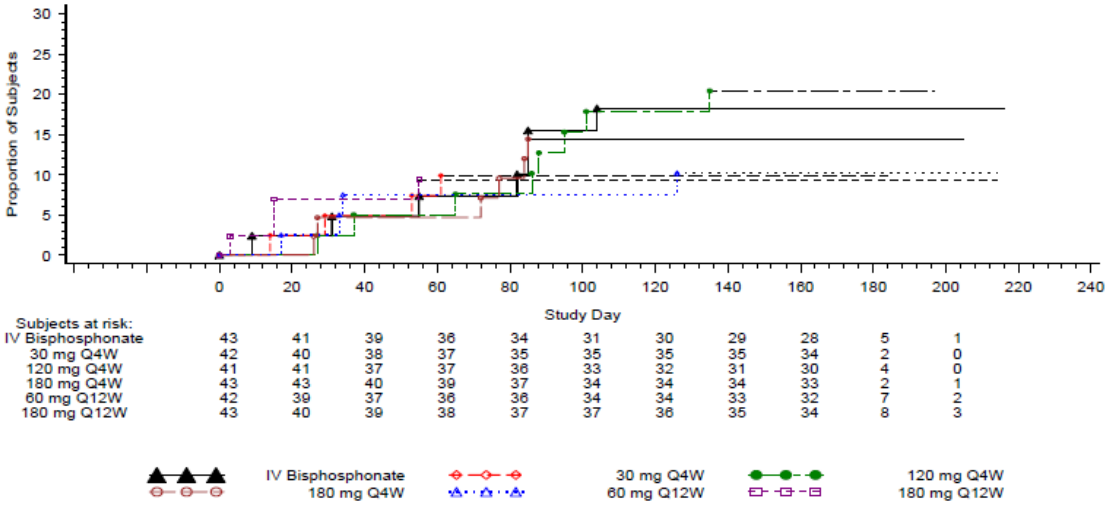
Dose response studies

The results of the two dose ranging trials (Studies 2004-0113 and 2004-0114) in terms of the drug effect on bone turnover markers have been previously discussed in the Clinical PD section of this AusPAR. The two dose response studies also included preliminary clinical efficacy endpoints of relevance to the current Australian submission (the proportion of subjects experiencing an SRE and time-to-first SRE) as secondary endpoints.

Study 2004-0113 was a dose response study in subjects with advanced breast cancer and no prior bisphosphonate exposure.

At the Week 13 and Week 25 follow-ups, the incidence of SREs was similar between the denosumab (9% and 12%, respectively) and zoledronic acid (14% and 16%, respectively) treatment groups. Most SREs (85% of events in either treatment group) had occurred prior to Week 13. The median time to the first SRE could not be calculated due to the low overall proportion of subjects who experienced SREs. No dose response pattern was observed in the Kaplan-Meier estimated incidence of SREs by Week 13 in the denosumab dosing groups (see Figure 14). Furthermore, no increased incidence of SREs was observed with the twelfth weekly dosing regimen of denosumab.

Figure 14. Kaplan-Meier Plot of Time to First SRE for Study 2004-0113



Study 2004-0114 was a dose response study in patients with advanced non-lung cancer who had been previously exposed to bisphosphonates.

Only a very small number of SREs were reported within the specified 25 weeks of follow-up in this trial. Six subjects (8.2% of 73) in the combined denosumab group and 6 subjects (17.1% of 35) in the zoledronic acid group reported an SRE.

Main (pivotal) studies

Methods

Objectives

The three pivotal studies had similar objectives and design with the subject population being the significant point of difference. Each study evaluated denosumab for the

prevention of SRE (a composite outcome measure of pathological fractures, radiation or surgery to bone and spinal cord compression). In all of the three pivotal studies the primary analysis was a non inferiority comparison with zoledronic acid. The primary and secondary endpoints reflect the objectives of the study program and are relevant to the sponsor's proposed indication. Each trial had a series of exploratory endpoints, many of which were not relevant to the sponsor's proposed indication. However, clinically relevant exploratory endpoints have also been included in the current evaluation.

Study Participants

Each of the three pivotal trials evaluated study medication (denosumab or zoledronic acid) in adult patients with known cancer and at least one bone metastasis (or osteolytic lesion in the case of multiple myeloma subjects).

Common inclusion criteria for the three pivotal studies were:

- Current or prior radiological evidence of at least one bone metastasis/lesion
- Eastern Cooperative Oncology Group (ECOG) performance status[22] of 2 or less
- Adequate organ function defined as:
    - aspartate aminotransferase/alanine aminotransferase AST/ALT< 5 x upper limit of normal,
    - Bilirubin < 2 x upper limit of normal,
    - Creatinine clearance >30mL/min by Cockcroft-Gault calculation, and
    - Corrected calcium levels of 2.0-2.9mmol/L as measured by the central laboratory

Significant common exclusion criterion included:

- Brain metastasis,
- Prior or current osteonecrosis or osteomyelitis of the jaw,
- Non-healed oral/dental surgery,
- Dental or jaw condition requiring oral surgery,
- Planned invasive dental procedures during the course of the study,
- Life expectancy of less than 6 months,
- Current or prior IV bisphosphonates (or oral bisphosphonates for bone metastasis), and
- Planned radiation or surgery to bone.

[22] The ECOG has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:

0 - Fully active, able to carry on all pre-disease performance without restriction

1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work

2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours

3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours

4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair

5 – Dead

Study 2005-0103 included men (>18 years of age) with histologically confirmed, hormone refractory prostate cancer.

Study 2005-0136 included adults with histologically or cytologically confirmed adenocarcinoma of the breast.

Study 2005-0244 included adults with histologically or cytologically confirmed 'advanced cancers' including various types of solid tumours (39% subjects had non-small cell lung cancer, 9% had renal cell carcinoma, and 6% had small cell lung cancer) or multiple myeloma (10% of subjects overall). All other tumour types individually comprised less than 5% of the enrolled population. Subjects with breast or prostate cancer were not included in this study.

Treatments

Study participants were randomised to receive denosumab 120 mg SC fourth weekly or intravenous zoledronic acid 4 mg fourth weekly in each of the pivotal trials.

Where relevant, adjuvant chemotherapy or hormonal therapy was permitted according to standards of care. While subjects were excluded for prior IV bisphosphonate use, prior oral bisphosphonate use was permissible in each of the pivotal trials unless the oral bisphosphonate treatment was prescribed for the indication of prevention of SREs.

Additional study specific treatments included:-

Study 2005-0103 required subjects to have serum testosterone < 50 ng/dL, either by surgical or medical castration (for example with GnRH agonists/antagonists).

Study 2005-0136 allowed patients to receive current chemotherapy (40% of participants overall) and/or hormonal therapy for breast cancer.

Study 2005-0244 contained a heterogeneous mix of advanced cancers. Concurrent treatment with relevant systemic anticancer therapy (chemotherapy, biologic therapy or hormonal therapy) was permitted. While it would seem unusual to combine multiple myeloma with other metastatic solid tumours (given the different disease process), this was done to provide consistency with an historical zoledronic acid/placebo study (see Statistical methods).

Endpoints

Each trial shared common primary and secondary endpoints as follows:

Primary endpoint was the time to first on study SRE as a non-inferiority analysis compared with zoledronic acid. The anticipated true hazard ratio (denosumab compared with zoledronic acid) for this analysis was 0.9 or less.

Secondary endpoints were:

- The time to first on study SRE as a superiority analysis compared with zoledronic acid, and
- The time to first-and-subsequent on study SRE (superiority, using multiple-event analysis)

A range of exploratory endpoints were specified for each study. Many of these endpoints are not relevant to the efficacy assessment of the sponsor's proposed indication and some of these endpoints were added or amended following commencement of the trial(s) from the original specified protocol.

Exploratory endpoints relevant to evaluating the proposed indication included:

- The time to first symptomatic SRE (this endpoint was not specified in the original protocols but was added secondary to comments from the FDA),
- The time to first on study radiation to bone, and
- Overall survival, disease progression in bone and overall disease progression.

Other exploratory endpoints that are not directly relevant to the proposed indication but are included within the text of the sponsor's proposed product information include:

- A composite outcome of time to first on study SRE or hypercalcaemia of malignancy (HCM), and
- A series of pain measures derived from the Brief Pain Inventory-Short Form (BPI-SF)[23] including changes from baseline in worst pain score, time to pain worsening, the proportion of patients reaching certain levels of pain severity as well as analgesic use.

Sample size

In each study, power calculations were performed on the basis of providing 90% power to demonstrate the primary endpoint and at least one of the secondary endpoints. An approximate number of 745 subjects experiencing a first on study SRE were calculated as providing adequate power for each study. This translated to the following planned sample sizes for each of the 3 pivotal studies:

Study 2005-0103. Planned sample size 1870 subjects; actual sample size 1901.

Study 2005-0136. Planned sample size 1960 subjects; actual sample size 2049.

Study 2005-0244. Planned sample size 1690 subjects; actual sample size 1779.

In Studies 2005-0103 and 2005-0136, the planned sample size was revised upwards from the originally specified protocol due to a lower than expected rate of SREs. Study 2005-0244 did not achieve the specified 745 SREs (601 subjects actually achieving a confirmed first on study SRE). However, it was felt that adequate power still existed to assess the primary (82% power) and secondary endpoints.

Randomisation

Subjects were randomised 1:1 to either denosumab or zoledronic acid by a stratified randomisation schedule using randomly permuted blocks developed prior to trial commencement. Within each stratum, an equal allocation ratio (1:1) occurred.

Stratification of randomisation occurred in each of the studies as follows:

Study 2005-0103 stratified by previous SRE (yes or no), PSA level (lesser or greater than 10 ng/mL) and chemotherapy within 6 weeks of randomisation (yes or no).

Study 2005-0136 stratified by previous SRE (yes or no), prior oral bisphosphonate use (yes or no), chemotherapy within 6 weeks of randomisation (yes or no) and region (Japan or other countries).

[23] The BPI-SF is a validated, widely used, self-administered questionnaire developed to assess the severity of pain and its impact on daily functions. It was originally designed to assess changes in osteoarthritis related pain over time but has been used in various conditions associated with chronic musculoskeletal pain. It has a scale ranging from 0-4.

Study 2005-0244 stratified by tumour type (non-small cell lung cancer or MM or other), previous SRE (yes or no) and systemic anticancer therapy (yes or no).

Blinding

All trials were double-blinded, utilising a double dummy approach with active agents/placebos provided in a blinded manner by the sponsor.

All subjects, investigators, site personnel and all sponsor study personnel remained blinded to treatment assignment except:

- A sponsor representative who maintained the randomisation schedule and otherwise not involved in the clinical trials, and
- Sponsor representatives involved in assessing serum samples for denosumab concentrations and detection of anti-denosumab antibodies.

The study investigators were able to access treatment assignment by contacting the Interactive Voice Response System (IVRS) if it were considered the knowledge of treatment was essential for further medical management. However, unblinding for any other reason was considered a protocol violation.

Statistical methods

Given the primary and secondary endpoints were time to event analyses, for subjects with no known SRE within the trial timeframe censoring was applied at the end of study date on the case report form or the primary analysis cut off date. This method was also applied to the four individual SRE subtypes. Primary and secondary endpoints were analysed using the full analysis set, with a pre specified per protocol analysis set used for sensitivity analysis.

The *primary efficacy endpoint* was analysed with a synthesis approach. [24] Essentially, this statistical method assumes a constant effect of the active comparator (zoledronic acid) from study to study. The design of the three pivotal studies was similar to historical studies involving zoledronic acid to attempt to facilitate a constant zoledronic acid effect compared with placebo. However, the sponsor only considered the constancy assumption violated if the effect of zoledronic acid compared with placebo was significantly different from study to study (differences in baseline demographics, study design and event rates were allowed). Historical estimates of hazard ratios and standard errors for zoledronic acid relative to placebo were combined with the estimates obtained in the trial for the purposes of performing the non-inferiority analysis. A Cox model with treatment groups as the independent variable, stratified by the randomisation stratification factors was used. Kaplan-Meier event rates with two sided confidence intervals were summarised at two time points in the studies. Sensitivity testing utilising the per protocol analysis set and the full analysis set with actual strata was performed. Covariate analyses on the primary endpoint were removed since no hazard ratios were available from the historical zoledronic acid studies for these covariate analyses.

Secondary efficacy endpoints were only evaluated if the primary endpoint was found to be significant with a level of significance (alpha) set at 0.05. *Time to first on study SRE* was tested for superiority by using the results of the Cox model for the primary endpoint directly in a Wald test. Level of significance (alpha) for secondary analyses was adjusted for multiplicity testing (testing the same data set with multiple tests) using the Hochberg principle available in Statistical Analysis System (SAS) software. Supportive analyses included an analysis with the per protocol analysis set, a Cox model to evaluate covariates,

[24] Hung HM, Wang S, Tsong Y. *et al*. Some fundamental issues with non-inferiority testing in active controlled trials. *Statistics Med* 2003; 22: 213-25.

a homogeneity evaluation of the individual type of SREs and an analysis with the full analysis set using actual stratum.

For testing of *Time to first SRE* and *Subsequent on study SRE*, an Andersen and Gill model with robust variance estimate (stratified by the randomisation stratification factors) was used. This accounted for the absolute number of SREs and the timing between the two consecutive events. A Nelson-Aalen estimate of cumulative mean number of SREs over time was plotted for each treatment arm. For an SRE to be considered a subsequent event it must have occurred at least 21 days after the previous SRE (so that, for example, surgery for a pathological fracture was not counted as a separate event). Supportive analyses included an analysis with the per protocol analysis set, an evaluation of covariates, an analysis without the 21 day window rule and analysis with the full analysis set using actual stratum.

Secondary analyses statistical methods were changed from the original protocol specified analysis in the following:

- Multiple event analysis changed from Prentice-Williams-Peterson to Andersen-Gill as requested by the US FDA.
- Covariates for assessment were revised to be consistent with other denosumab studies.

Multiple changes to the statistical methods for e*xploratory endpoints* were made; however, most of these endpoints are not relevant to the evaluation of the current Australian submission. The significance level for each exploratory endpoint was 0.05 without adjusting for multiplicity.

The Kaplan-Meier method was used to estimate mean and quartiles of time to event variables (both primary and secondary) and Kaplan-Meier curves were presented graphically up until < 50 subjects were at risk in the combined treatment groups.

Participant flow

Subjects were considered randomised once a randomisation number was assigned. Prior to unblinding, a decision was made to exclude subjects from all analysis when Institutional Review Board (IRB) review activities and oversight were not ensured (three subjects in each of the three individual pivotal trials).

The majority (up to 80%) of subjects withdrew from study treatment and follow-up before the conclusion of the primary analysis cut off date and with the most common reasons were death, consent withdrawn and disease progression. The case report form (CRF) for the trials stated that 'disease progression' should not be selected unless the subject's disease was so severe that they did not wish to receive further investigational product or could not continue with study assessments. Reasons for study discontinuation are summarised in Table 10.

Table 10. Reasons for Study Discontinuation for Pivotal Studies

	Study 20050136		Study 20050244		Study 20050103		Overall	
	Zoledronic Acid 4 mg Q4W n (%)	Denosumab 120 mg Q4W n (%)	Zoledronic Acid 4 mg Q4W n (%)	Denosumab 120 mg Q4W n (%)	Zoledronic Acid 4 mg Q4W n (%)	Denosumab 120 mg Q4W n (%)	Zoledronic Acid 4 mg Q4W n (%)	Denosumab 120 mg Q4W n (%)
Randomized	1020	1026	890	886	951	950	2861	2862
On study through primary data analysis cut-off date	461 (45.2)	468 (45.6)	178 (20.0)	180 (20.3)	208 (21.9)	228 (24.0)	847 (29.6)	876 (30.6)
Discontinued prior to primary data analysis cut-off date	559 (54.8)	558 (54.4)	712 (80.0)	706 (79.7)	743 (78.1)	722 (76.0)	2014 (70.4)	1986 (69.4)
Death	169 (16.6)	174 (17.0)	316 (35.5)	310 (35.0)	269 (28.3)	294 (30.9)	754 (26.4)	778 (27.2)
Consent withdrawn[a]	117 (11.5)	118 (11.5)	143 (16.1)	124 (14.0)	164 (17.2)	147 (15.5)	424 (14.8)	389 (13.6)
Disease progression	124 (12.2)	124 (12.1)	104 (11.7)	126 (14.2)	113 (11.9)	117 (12.3)	341 (11.9)	367 (12.8)
Subject request[b]	57 (5.6)	61 (5.9)	31 (3.5)	22 (2.5)	75 (7.9)	52 (5.5)	163 (5.7)	135 (4.7)
Adverse event	43 (4.2)	28 (2.7)	48 (5.4)	36 (4.1)	43 (4.5)	56 (5.9)	134 (4.7)	120 (4.2)
Other	21 (2.1)	18 (1.8)	36 (4.0)	44 (5.0)	42 (4.4)	33 (3.5)	99 (3.5)	95 (3.3)
Lost to follow-up	7 (0.7)	8 (0.8)	16 (1.8)	22 (2.5)	13 (1.4)	9 (0.9)	36 (1.3)	39 (1.4)
Noncompliance	4 (0.4)	10 (1.0)	15 (1.7)	17 (1.9)	14 (1.5)	7 (0.7)	33 (1.2)	34 (1.2)
Administrative decision	15 (1.5)	14 (1.4)	1 (0.1)	2 (0.2)	4 (0.4)	1 (0.1)	20 (0.7)	17 (0.6)
Protocol deviation	0 (0.0)	2 (0.2)	0 (0.0)	2 (0.2)	4 (0.4)	3 (0.3)	4 (0.1)	7 (0.2)
Ineligibility determined	2 (0.2)	1 (<0.1)	2 (0.2)	1 (0.1)	2 (0.2)	3 (0.3)	6 (0.2)	5 (0.2)

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Percentages based on number of subjects randomized
[a] Subject withdrew full consent to participate in study any longer, including long term follow-up
[b] Subject does not wish to attend any further Q4W assessments, but agrees to be contacted for survival follow-up

Recruitment

Recruitment and primary analysis cut off dates are as follows:

- Study 2005-0103: 12 May 2006 to 30 October 2009.
- Study 2005-0136: 27 April 2006 to 6 March 2009.
- Study 2005-0244: 21 June 2006 to 30 April 2009.

Conduct of the study

Three subjects in each study were excluded from analysis due to institutional review board (IRB) review activities and oversight not being ensured (such as proper informed consent not obtained). Two study sites were prematurely terminated across all three Phase III SRE studies due to ICH GCP violations in Studies 2005-0103 and 2005-0136. Other protocol violations were generally low or of limited significance and balanced between groups.

Baseline data

Baseline demographic and disease history characteristics were well matched between groups in each trial and are illustrated in Tables 12-13.

Table 12. Baseline Demographic Characteristics of Subjects for Pivotal Studies

	Study 20050136		Study 20050244		Study 20050103		Overall	
	Zoledronic Acid 4 mg Q4W (N = 1020)	Denosumab 120 mg Q4W (N = 1026)	Zoledronic Acid 4 mg Q4W (N = 890)	Denosumab 120 mg Q4W (N = 886)	Zoledronic Acid 4 mg Q4W (N = 951)	Denosumab 120 mg Q4W (N = 950)	Zoledronic Acid 4 mg Q4W (N = 2861)	Denosumab 120 mg Q4W (N = 2862)
Sex - n (%)								
Female	1011 (99.1)	1018 (99.2)	338 (38.0)	298 (33.6)	0 (0.0)	0 (0.0)	1349 (47.2)	1316 (46.0)
Male	9 (0.9)	8 (0.8)	552 (62.0)	588 (66.4)	951 (100.0)	950 (100.0)	1512 (52.8)	1546 (54.0)
Ethnic group / race - n (%)								
White or Caucasian	813 (79.7)	822 (80.1)	770 (86.5)	770 (86.9)	810 (85.2)	829 (87.3)	2393 (83.6)	2421 (84.6)
Black or African American	25 (2.5)	26 (2.5)	29 (3.3)	20 (2.3)	35 (3.7)	38 (4.0)	89 (3.1)	84 (2.9)
Hispanic or Latino	59 (5.8)	59 (5.8)	36 (4.0)	49 (5.5)	57 (6.0)	45 (4.7)	152 (5.3)	153 (5.3)
Asian	37 (3.6)	32 (3.1)	44 (4.9)	36 (4.1)	26 (2.7)	22 (2.3)	107 (3.7)	90 (3.1)
Japanese	69 (6.8)	70 (6.8)	1 (0.1)	3 (0.3)	0 (0.0)	0 (0.0)	70 (2.4)	73 (2.6)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)	0 (0.0)
Ethnic group / race - n (%)								
Native Hawaiian or Other Pacific Islander	1 (<0.1)	1 (<0.1)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	2 (<0.1)	2 (<0.1)
Other	16 (1.6)	16 (1.6)	8 (0.9)	8 (0.9)	22 (2.3)	15 (1.6)	46 (1.6)	39 (1.4)
Age (years)								
n	1020	1026	890	886	951	950	2861	2862
Mean	56.6	56.8	60.6	59.3	71.0	70.5	62.6	62.1
SD	11.6	11.5	10.7	11.4	8.4	8.7	12.1	12.2
Median	56.0	57.0	61.0	60.0	71.0	71.0	63.0	63.0
Q1, Q3	49.0, 65.0	49.0, 65.0	53.0, 69.0	52.0, 67.0	66.0, 77.0	64.0, 77.0	54.0, 72.0	54.0, 71.0
Min, Max	24, 90	27, 91	22, 87	18, 89	38, 91	40, 93	22, 91	18, 93
Age group - n (%)								
< 50 years	287 (28.1)	275 (26.8)	128 (14.4)	160 (18.1)	5 (0.5)	9 (0.9)	420 (14.7)	444 (15.5)
≥ 50 years	733 (71.9)	751 (73.2)	762 (85.6)	726 (81.9)	946 (99.5)	941 (99.1)	2441 (85.3)	2418 (84.5)
Geriatric age group - n (%)								
≥ 65 years	266 (26.1)	275 (26.8)	336 (37.8)	299 (33.7)	735 (77.3)	697 (73.4)	1337 (46.7)	1271 (44.4)
≥ 75 years	63 (6.2)	61 (5.9)	74 (8.3)	74 (8.4)	347 (36.5)	338 (35.6)	484 (16.9)	473 (16.5)

Table 13. Baseline Disease Characteristics of Subjects in pivotal studies

	Study 20050136		Study 20050244		Study 20050103		Overall	
	Zoledronic Acid 4 mg Q4W (N = 1020)	Denosumab 120 mg Q4W (N = 1026)	Zoledronic Acid 4 mg Q4W (N = 890)	Denosumab 120 mg Q4W (N = 886)	Zoledronic Acid 4 mg Q4W (N = 951)	Denosumab 120 mg Q4W (N = 950)	Zoledronic Acid 4 mg Q4W (N = 2861)	Denosumab 120 mg Q4W (N = 2862)
ECOG at study entry - n (%)								
0	488 (47.8)	504 (49.1)	236 (26.5)	240 (27.1)	426 (44.8)	418 (44.0)	1150 (40.2)	1162 (40.6)
1	444 (43.5)	451 (44.0)	492 (55.3)	508 (57.3)	460 (48.4)	464 (48.8)	1396 (48.8)	1423 (49.7)
2	82 (8.0)	68 (6.6)	157 (17.6)	136 (15.3)	65 (6.8)	68 (7.2)	304 (10.6)	272 (9.5)
3	2 (0.2)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)	1 (<0.1)
Missing	4 (0.4)	2 (0.2)	5 (0.6)	2 (0.2)	0 (0.0)	0 (0.0)	9 (0.3)	4 (0.1)
Tumor type - n (%)								
Breast Cancer	1020 (100.0)	1026 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1020 (35.7)	1026 (35.8)
Prostate Cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	951 (100.0)	950 (100.0)	951 (33.2)	950 (33.2)
Multiple Myeloma	0 (0.0)	0 (0.0)	93 (10.4)	87 (9.8)	0 (0.0)	0 (0.0)	93 (3.3)	87 (3.0)
Other	0 (0.0)	0 (0.0)	797 (89.6)	799 (90.2)	0 (0.0)	0 (0.0)	797 (27.9)	799 (27.9)

	Study 20050136		Study 20050244		Study 20050103		Overall	
	Zoledronic Acid 4 mg Q4W (N = 1020)	Denosumab 120 mg Q4W (N = 1026)	Zoledronic Acid 4 mg Q4W (N = 890)	Denosumab 120 mg Q4W (N = 886)	Zoledronic Acid 4 mg Q4W (N = 951)	Denosumab 120 mg Q4W (N = 950)	Zoledronic Acid 4 mg Q4W (N = 2861)	Denosumab 120 mg Q4W (N = 2862)
Time from initial cancer diagnosis to first bone metastasis (months)								
n	1020	1026	885	884	951	948	2856	2858
Mean	52.73	52.83	14.30	13.30	42.53	43.33	37.43	37.45
SD	58.80	58.17	31.98	28.67	47.76	51.88	50.67	51.35
Median	35.44	32.81	2.86	2.07	24.48	24.49	16.52	16.62
Q1, Q3	8.64, 75.50	7.00, 78.65	0.03, 14.52	-0.03, 15.03	1.74, 71.56	2.00, 64.79	0.95, 57.26	0.89, 54.74
Min, Max	-4.7, 343.9	-2.1, 393.5	-38.2, 390.9	-16.2, 263.6	-16.9, 248.0	-12.2, 481.8	-38.2, 390.9	-16.2, 481.8
Time from first bone metastasis to randomization (months)								
n	1020	1026	886	884	951	949	2857	2859
Mean	5.70	5.90	4.71	4.36	13.18	12.06	7.88	7.47
SD	12.77	11.63	10.44	10.75	20.56	18.34	15.71	14.37
Median	2.02	2.10	1.84	1.74	5.19	3.94	2.30	2.17
Q1, Q3	1.08, 4.95	1.02, 5.13	0.89, 4.07	0.92, 3.78	1.31, 16.10	1.22, 15.67	1.05, 7.62	1.02, 7.10
Min, Max	0.1, 191.0	0.0, 138.1	0.1, 129.7	0.1, 152.2	0.0, 156.7	0.0, 207.3	0.0, 191.0	0.0, 207.3

	Study 20050136		Study 20050244		Study 20050103		Overall	
	Zoledronic Acid 4 mg Q4W (N = 1020)	Denosumab 120 mg Q4W (N = 1026)	Zoledronic Acid 4 mg Q4W (N = 890)	Denosumab 120 mg Q4W (N = 886)	Zoledronic Acid 4 mg Q4W (N = 951)	Denosumab 120 mg Q4W (N = 950)	Zoledronic Acid 4 mg Q4W (N = 2861)	Denosumab 120 mg Q4W (N = 2862)
Number of metastatic lesions in bone (by central read of skeletal survey) - n (%)								
≤ 2	780 (76.5)	784 (76.4)	746 (83.8)	749 (84.5)	623 (65.5)	632 (66.5)	2149 (75.1)	2165 (75.6)
> 2	240 (23.5)	242 (23.6)	144 (16.2)	137 (15.5)	328 (34.5)	318 (33.5)	712 (24.9)	697 (24.4)
Osteolytic/non-osteolytic lesion (by central read of skeletal survey) - n (%)								
Osteolytic	139 (13.6)	152 (14.8)	212 (23.8)	196 (22.1)	39 (4.1)	32 (3.4)	390 (13.6)	380 (13.3)
Non-osteolytic	881 (86.4)	874 (85.2)	678 (76.2)	690 (77.9)	912 (95.9)	918 (96.6)	2471 (86.4)	2482 (86.7)
Osteoblastic/non-osteoblastic lesion (by central read of skeletal survey) - n (%)								
Osteoblastic	285 (27.9)	281 (27.4)	130 (14.6)	151 (17.0)	537 (56.5)	601 (63.3)	952 (33.3)	1033 (36.1)
Non-osteoblastic	735 (72.1)	745 (72.6)	760 (85.4)	735 (83.0)	414 (43.5)	349 (36.7)	1909 (66.7)	1829 (63.9)

	Study 20050136		Study 20050244		Study 20050103		Overall	
	Zoledronic Acid 4 mg Q4W (N = 1020)	Denosumab 120 mg Q4W (N = 1026)	Zoledronic Acid 4 mg Q4W (N = 890)	Denosumab 120 mg Q4W (N = 886)	Zoledronic Acid 4 mg Q4W (N = 951)	Denosumab 120 mg Q4W (N = 950)	Zoledronic Acid 4 mg Q4W (N = 2861)	Denosumab 120 mg Q4W (N = 2862)
Presence of visceral metastases - n (%)	525 (51.5)	552 (53.8)	448 (50.3)	474 (53.5)	181 (19.0)	161 (16.9)	1154 (40.3)	1187 (41.5)
Liver - n (%)	182 (17.8)	211 (20.6)	167 (18.8)	171 (19.3)	20 (2.1)	16 (1.7)	369 (12.9)	398 (13.9)
Lung - n (%)	210 (20.6)	216 (21.1)	162 (18.2)	239 (27.0)	32 (3.4)	26 (2.7)	404 (14.1)	481 (16.8)
Other - n (%)	369 (36.2)	369 (36.0)	340 (38.2)	319 (36.0)	153 (16.1)	141 (14.8)	862 (30.1)	829 (29.0)

*Numbers Analysed*The number of subjects analysed in the individual pivotal Phase III trials including full analysis set (used for primary and secondary endpoint analyses) and per protocol analysis set (used for secondary endpoint sensitivity testing) are summarised in Table 14. The full analysis set included all randomised patients (an intention to treat (ITT) basis), excluding three patients in each trial for which proper informed consent was not obtained prior to receiving the investigational product. The per protocol set included all patients that met the key eligibility criteria and received at least one dose of study treatment. Significant on study protocol violations (such as unapproved anti resorptive medications, incorrect investigational product, not receiving three consecutive doses of study treatment except for adverse events or predefined laboratory value abnormalities) for the per protocol set lead to censoring (excluding from the analysis) of the subject's data 36 days after the protocol violation.

Table 14. Numbers analysed in pivotal trials

Study ID	Full Analysis Set		Per protocol Analysis Set	
	D	Z	D	Z
2005-0103	950	951	935	939
2005-0136	1026	1020	1017	1012
2005-0244	886	890	871	874

Key: D=denosumab, Z=zoledronic acid

Results

Primary efficacy endpoint

In each of the three pivotal studies, the primary efficacy endpoint was found to be significant (Study 2005-0103 p=0.0002; Study 2005-0136 p<0.001; Study 2005-0244 p=0.0007). Pre-defined sensitivity testing supported the primary analyses. Kaplan-Meier curves for the primary efficacy endpoint in the three key studies are displayed in Figures 15-17.

The results indicate that denosumab has non inferior efficacy compared with zoledronic acid for the prevention of first SRE in subjects with malignancy and bone metastasis. This is a clinically significant result as zoledronic acid has been established as standard therapy for this indication in many countries. The subgroup analysis of Study 2005-0244 is pertinent to the consideration of the indication wording for denosumab and is discussed in detail later in this AusPAR.

Secondary efficacy endpoints

Given the significant result of the primary efficacy endpoints, secondary endpoint testing was performed for each of the three studies. The individual studies are discussed below.

Study 2005-0103 (prostate cancer). In this study, denosumab significantly decreased the risk of developing a first on study SRE (HR 0.82; 95% CI 0.71-0.95, p=0.0085 for superiority). Results were consistent with the per protocol analysis set and the full analysis set with actual strata. Median time to first on study SRE was 20.7 months versus 17.1 months. Homogeneity testing did not suggest inconsistent effect across the SRE components (p=0.7059). Figure 15 illustrates the number of individual SRE events. Time to first and subsequent on study SRE was also significantly decreased with denosumab (rate ratio 0.82, 95% CI 0.71-0.94, p=0.0044).

While superiority testing was found to be significant for the secondary endpoints, the absolute and relative differences in event rates are modest compared with zoledronic acid.

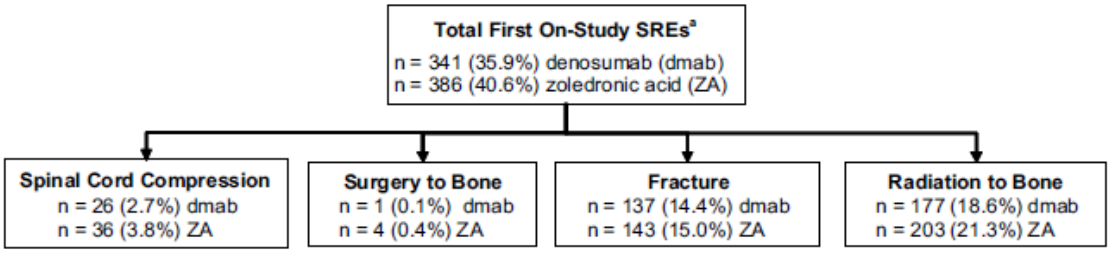
The efficacy endpoints are summarised in Table 15. Kaplan-Meier curves for the primary efficacy endpoint are displayed in Figure 16.

Table 15. Summary of Efficacy Endpoints for Study 2005-0103.

Endpoint	Denosumab vs Zoledronic Acid Hazard Ratio or Rate Ratio[a]			
	Pt Est	(95% CI)	p-value (unadjusted)	p-value (adjusted)
Time to first on-study SRE (noninferiority)	0.82	(0.71, 0.95)	0.0002	0.0002
Time to first on-study SRE (superiority)	0.82	(0.71, 0.95)	0.0085	0.0085
Time to first and subsequent on-study SRE	0.82	(0.71, 0.94)	0.0044	0.0085
Time to first on-study SRE or HCM	0.83	(0.72, 0.96)	0.0134	
Time to radiation in bone	0.78	(0.66, 0.94)	0.0071	
Overall survival	1.03	(0.91, 1.17)	0.6511	
Time to disease progression in bone	0.92	(0.80, 1.06)	0.2629	
Time to overall disease progression	1.06	(0.95, 1.18)	0.3000	
Time to overall disease progression or death (any cause)	1.05	(0.95, 1.16)	0.3542	
Time to first symptomatic SRE	0.78	(0.66, 0.93)	0.0051	

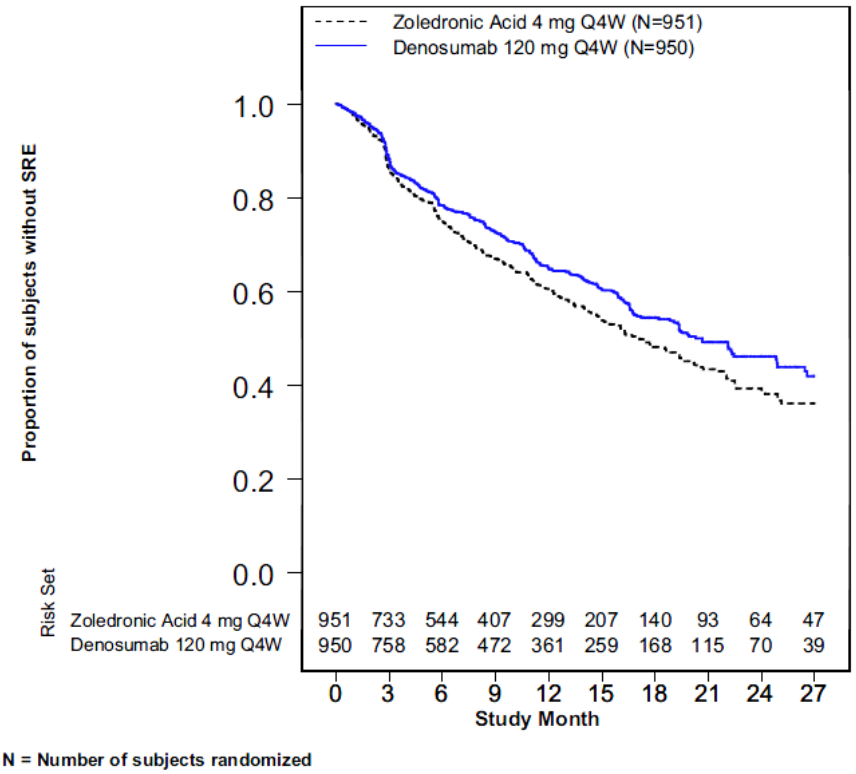
HCM = hypercalcemia of malignancy; SRE = skeletal-related event
[a] Hazard ratio or rate ratio < 1 favors denosumab

Figure 15. First On study SRE for Study 2005-0103



n = number of subjects with an event (% based on total number of subjects randomized)
[a] First on-study SRE was determined hierarchically (spinal cord compression, surgery, fracture, radiation) for events occurring on same day.

Figure 16. Kaplan-Meier Curve for Time to First On study SRE for Study 2005-0103



N = Number of subjects randomized

Study 2005-0136 (breast cancer). In this study, denosumab significantly reduced the risk of a first on study SRE compared with zoledronic acid (HR 0.82, 95% CI 0.71-0.95, p=0.01). Results were consistent with the per protocol analysis set and the full analysis set with actual strata. Time to first and subsequent on study SRE was also significantly improved with denosumab (rate ratio 0.77, 95% CI 0.66-0.89; p=0.0006). Absolute rates of the individual SRE sub components are illustrated in Figure 19. Homogeneity testing did not find any inconsistency across the four SRE components (p=0.47).

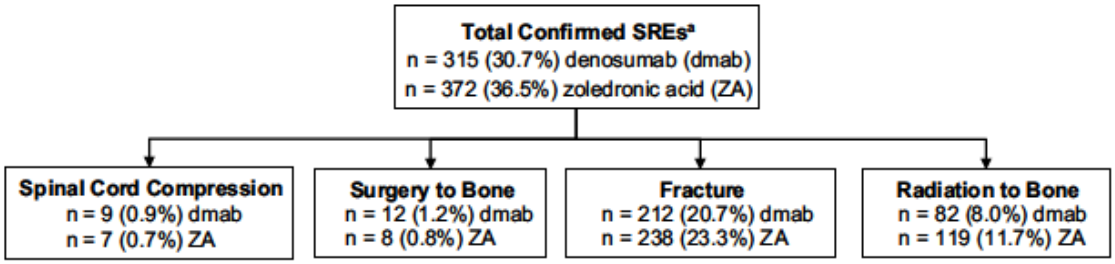
The results suggest that efficacy of denosumab for the prevention of SREs in superior to zoledronic acid, although once again, the magnitude of the superiority is modest. A summary of the efficacy endpoints is shown in Table 16. Kaplan-Meier curves for the primary efficacy endpoint are displayed in Figure 18.

Table 16. Summary of Efficacy Endpoints for Study 2005-0136

Endpoint	Denosumab vs Zoledronic Acid Hazard Ratio or Rate Ratio[a]			
	Pt Est	(95% CI)	p-value (unadjusted)	p-value (adjusted)
Time to first on-study SRE (noninferiority)	0.82	(0.71, 0.95)	< 0.0001	< 0.0001
Time to first on-study SRE (superiority)	0.82	(0.71, 0.95)	0.0101	0.0101
Time to first and subsequent on-study SRE	0.77	(0.66, 0.89)	0.0006	0.0012
Time to first on-study SRE or HCM	0.82	(0.70, 0.95)	0.0074	
Time to radiation in bone	0.74	(0.59, 0.94)	0.0121	
Overall survival	0.95	(0.81, 1.11)	0.4921	
Time to disease progression in bone	0.99	(0.87, 1.13)	0.8674	
Time to overall disease progression	1.00	(0.89, 1.11)	0.9302	
Time to overall disease progression or death (any cause)	1.00	(0.90, 1.11)	0.9551	
Time to first symptomatic SRE	0.76	(0.61, 0.93)	0.0092	

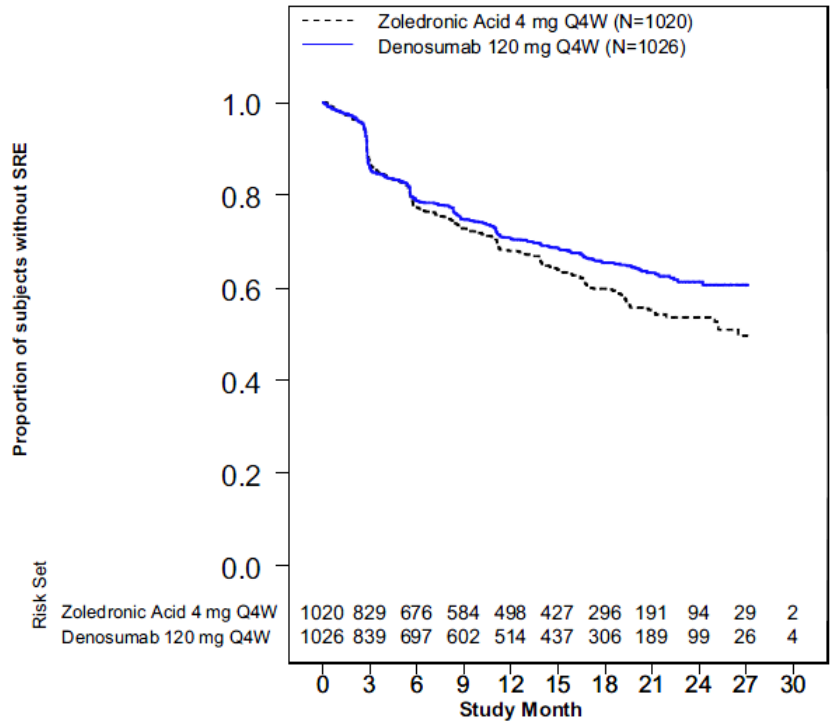
HCM = hypercalcemia of malignancy; SRE = skeletal-related event
[a] Hazard ratio or rate ratio < 1 favors denosumab

Figure 17. First On study SRE for Study 2005-0136.



n = number of subjects with an event (% based on total number of subjects randomized)
[a] First on-study SRE was determined hierarchically (spinal cord compression, surgery, fracture, radiation) for events occurring on same day.

Figure 18. Kaplan-Meier Curve for Time to First On study SRE for Study 2005-0136



N = Number of subjects randomized

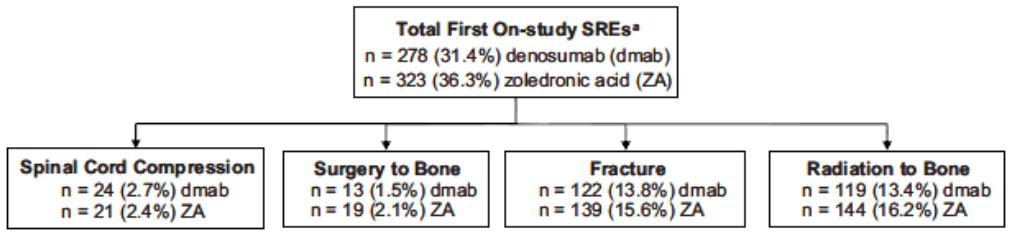
Study 2005-0244 (various cancers including non-small cell lung cancer and MM). Although a trend was seen (HR 0.84, 95% CI 0.71-0.98), secondary efficacy endpoint analysis for superiority compared with zoledronic acid in this trial did not achieve significance (p=0.031 unadjusted) when adjusted (p=0.0619) for multiplicity testing (given the same data was simultaneously tested both for primary and secondary endpoints). Testing using the per protocol set and the full analysis set with actual strata was consistent with the primary analysis. Homogeneity testing did not find an inconsistent effect across the four SRE components (p=0.79). Absolute numbers of SRE events are outlined in Figure 19. Time to first and Subsequent on study SRE also did not achieve significance (rate ratio 0.90, 95% CI 0.77-1.04, p=0.1447). A summary of the efficacy endpoints is given in Table 17. Kaplan-Meier curves for the primary efficacy endpoint are displayed in Figure 20.

Table 17. Summary of Efficacy Endpoints for Study 2004-0244

Endpoint	Denosumab vs Zoledronic Acid Hazard Ratio or Rate Ratio[a]			
	Pt Est	(95% CI)	p-value (unadjusted)	p-value (adjusted)
Time to first on-study SRE (noninferiority)	0.84	(0.71, 0.98)	0.0007	0.0007
Time to first on-study SRE (superiority)	0.84	(0.71, 0.98)	0.0309	0.0619
Time to first and subsequent on-study SRE	0.90	(0.77, 1.04)	0.1447	0.1447
Time to radiation in bone	0.78	(0.63, 0.97)	0.0256	
Time to first on-study SRE or HCM	0.83	(0.71, 0.97)	0.0215	
Overall survival	0.95	(0.83, 1.08)	0.4305	
Time to overall disease progression	1.00	(0.89, 1.12)	0.9979	
Time to overall disease progression or death (any cause)	1.01	(0.91, 1.13)	0.8499	
Time to disease progression in bone	0.98	(0.83, 1.16)	0.8188	
Time to first symptomatic SRE	0.84	(0.69, 1.02)	0.0738	

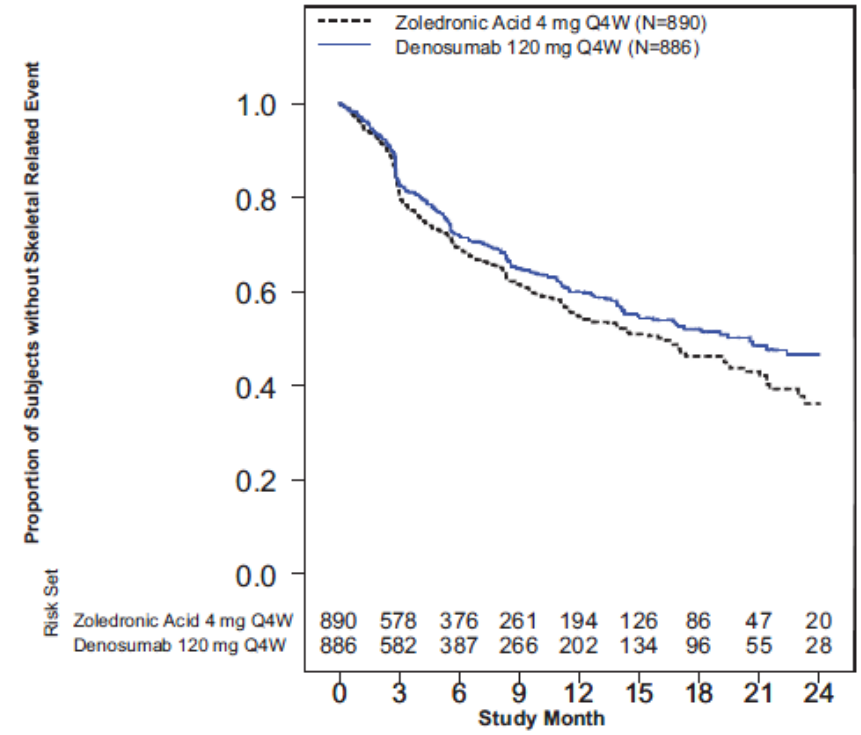
HCM = hypercalcemia of malignancy; SRE = skeletal-related event
[a] Hazard ratio or Rate Ratio < 1 favors denosumab

Figure 19. First On study SRE for Study 2005-0244



n = number of subjects with an event (% based on total number of subjects randomized)
[a] First on-study SRE was determined hierarchically (spinal cord compression, surgery, fracture, radiation) for events occurring on same day.

Figure 20. Kaplan-Meier Curve for Time to First On study SRE for Study 2005-0244



N = Number of subjects randomized

Significant Exploratory Endpoints

Time to first on study SRE or HCM did not add significantly to the results in any of the studies, as the addition of HCM to the composite endpoint did not lead to a significantly greater number of events. As such, this composite endpoint was essentially driven by SREs. In any case, the sponsor has not sought an indication for prevention of HCM and therefore this endpoint is not of relevance to this evaluation.

Other relevant exploratory endpoints are discussed below.

Study 2005-0103 (prostate cancer). As seen in Table 15, of the relevant exploratory endpoints, time to radiation in bone (HR 0.78, 95% CI 0.66-0.94), p=0.0071) and time to first symptomatic SRE (HR 0.78, 95% CI 0.66-0.93, p=0.0051) were found to be significant. However, no difference in overall survival or disease progression (overall or bone specific) was observed.

Study 2005-0136 (breast cancer). Relevant exploratory efficacy endpoints are summarised in Table 16. Of note, time to radiation in bone (HR 0.74, 95% CI 0.59-0.94; p=0.012) and time to first symptomatic SRE (HR 0.76, 95% CI 0.61-0.93; p=0.009) were significantly improved with denosumab compared with zoledronic acid. Again, no difference for overall survival or disease progression, including disease progression in bone, was found with denosumab treatment compared with zoledronic acid.

Study 2005-0244 (Other solid tumours and multiple myeloma). Clinically relevant exploratory endpoints are summarised in Table 17. Of note, time to radiation in bone (HR 0.78, 95% CI 0.63-0.97, p=0.0256) reached significance. However, time to first symptomatic SRE, overall survival and time to disease progression (overall disease and bone specific) were not significantly different to zoledronic acid.

Changes in BPI-SF pain scores and analgesic use

In the integrated analysis, approximately half of all patients (in either the denosumab or zoledronic acid treatment groups) had mild or no pain at worst at baseline and on average were using 1.3-1.5 analgesics. Using the integrated population dataset and assessed by AUC, the change in worst pain score up until Week 41 was similar between the two active treatment groups with a point estimate for treatment difference being 0.02 (95% CI -0.07, 0.12; p=0.6072). Furthermore, the mean change in BPI-SF worst pain scores was similar between the two treatments for each of the three pivotal studies.

However, in the integrated analysis, denosumab treatment showed a statistically significant delay in the median time to worsening pain (defined as at least a two point increase from baseline in worst pain score) compared with zoledronic acid (181 days for denosumab and 169 days for zoledronic acid; HR 0.92 [95% CI 0.86, 0.99] with p=0.0263). Nonetheless, this result is of little clinical relevance. Similarly, in the integrated analysis, the median time to moderate or severe worst pain (defined as a score > 4) was slightly longer for denosumab treatment compared with zoledronic acid (65 days versus 59 days: HR 0.91 [95% CI 0.85, 0.96] with p=0.0016).

However, the integrated analysis did not show a consistent treatment effect as the median time to pain improvement and mean analgesic use was similar for both treatment groups. In addition, the pain score analyses were performed on an ad or post hoc basis and because they do not demonstrate a uniformly consistent, clinically significant treatment effect in favour of denosumab compared with zoledronic acid, consideration of their removal from the proposed Australian PI was recommended. Furthermore the claims of a potential treatment differential analgesic effect are peripheral to the sponsors proposed indication wording.

Ancillary analyses

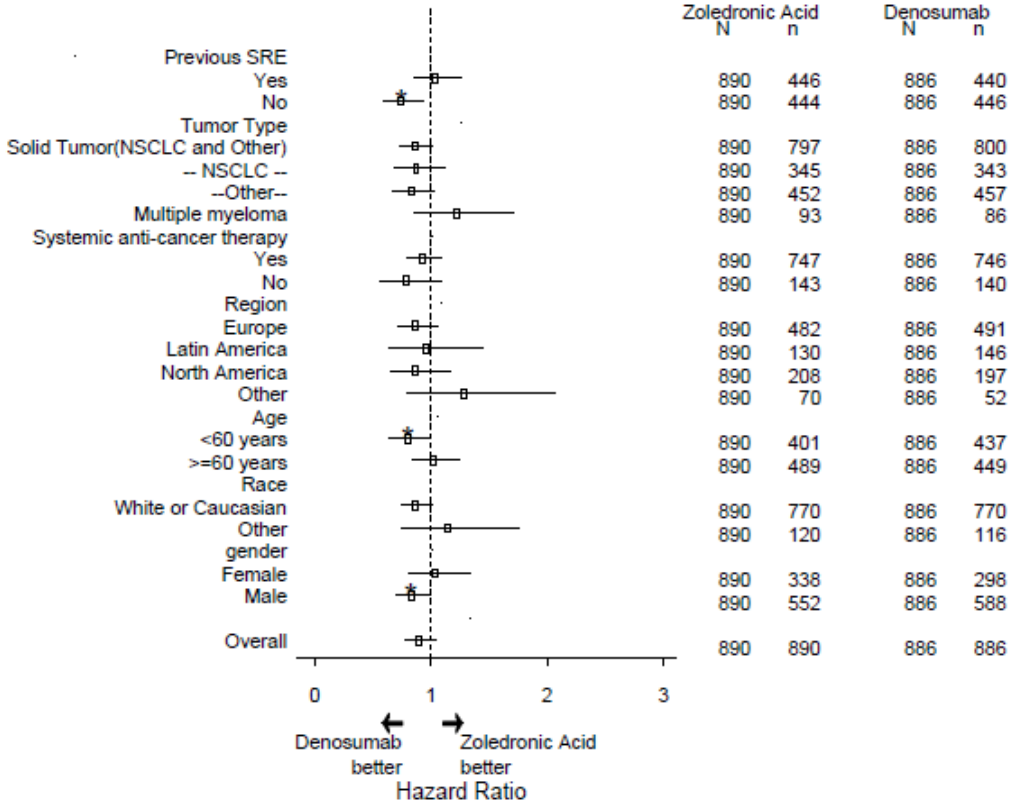
Subgroup Analysis by Tumour Type for Study 2005-0244

Given the range of different malignancies enrolled in *Study 2005-0244*, a pre specified subgroup analysis of the tumour subtypes was performed (divided into four categories). The Forest plot for this analysis is provided in Figure 21. While the statistical power has been lost due to reduced sample size, it would appear that the trend to superiority of denosumab compared to zoledronic acid holds for non small lung cancer and for 'Other' tumours (comprising a large range of solid tumours). Given the confidence intervals are wide and cross a hazard ratio (HR) of 1, multiple myeloma statistically has equivalent efficacy for the two drugs on this analysis, although the trend favours zoledronic acid. A further post hoc subgroup analysis was performed for solid tumours, both as a group and as individual malignancies (where there were at least 10 subjects; see Figure 22). Given the small sample sizes and large confidence intervals which all cross the HR of 1, the analysis of individual malignancies does not contribute significantly. As a group, solid tumours do appear to have modest benefit of denosumab over zoledronic acid for the prevention of SREs. A summary of the effect of denosumab compared with zoledronic for each tumour type across the three studies is provided in Table 18.

Of particular relevance to this submission is the subgroup analysis of overall survival by tumour type for Study 2005-0244, as a prominent difference in survival of patients given denosumab compared with zoledronic acid in the MM group was seen (HR 2.26, 95% CI 1.13-4.5, illustrated in Figure 23). Although this was a post hoc analysis, the extent of the difference is concerning for the potential licensing of denosumab, particularly given the different disease process that exists in multiple myeloma. A differential effect in response is also biologically plausible. Differences in overall survival were noted in other tumour types (for example, non small lung cancer HR 0.79, 95% CI 0.65-0.95, bladder cancer HR

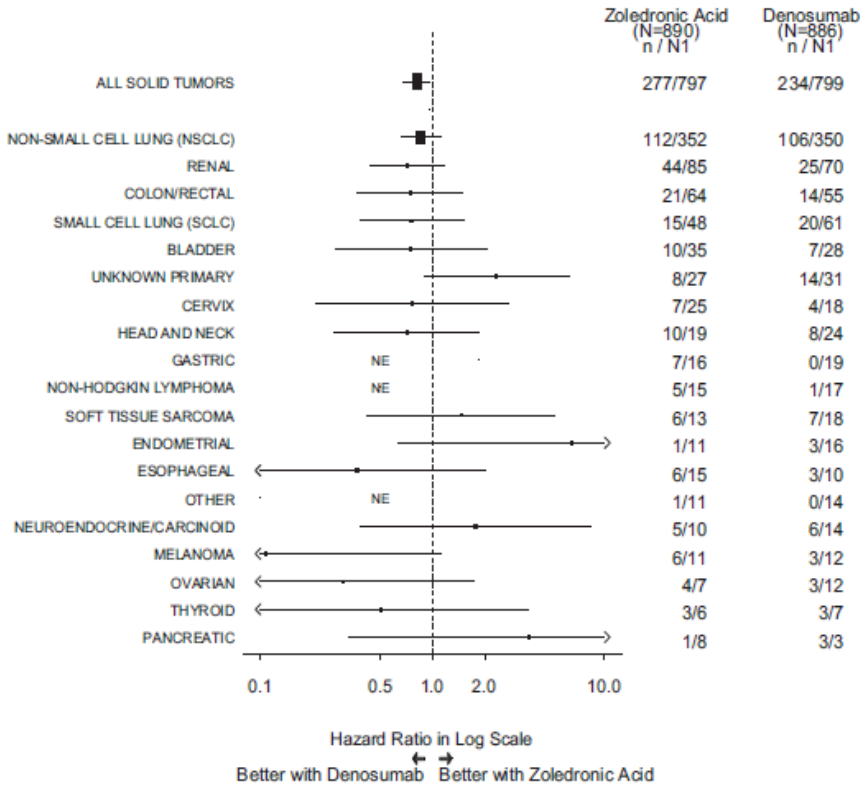
0.45 95% CI 0.22, 0.92) and endometrial cancer (HR 10.26, 95% CI 1.29-81.61). The number of subjects in the bladder and endometrial cancer groups were very small and baseline differences in the non small cell lung cancer exist (ECOG score of 2; 15.7% denosumab and 19.7% zoledronic acid) and drawing definitive conclusions on a post hoc analysis would be premature as the statistical robustness of these analyses are not sufficient for this purpose.

Figure 21. Forest Plot of Time to First on study SRE by Subgroup including Pre-specified Tumour Types for Study 2005-0244



Hazard ratio and 95% CI from a Cox proportional hazards model stratified by the randomization stratification variables Subgroup of Multiple Myeloma vs Solid Tumors (NSCLC and Others combined) was added

Figure 22. Forest Plot of Time to First on study SRE for Study 2005-0244 by Solid Tumour Type (Post hoc analysis)



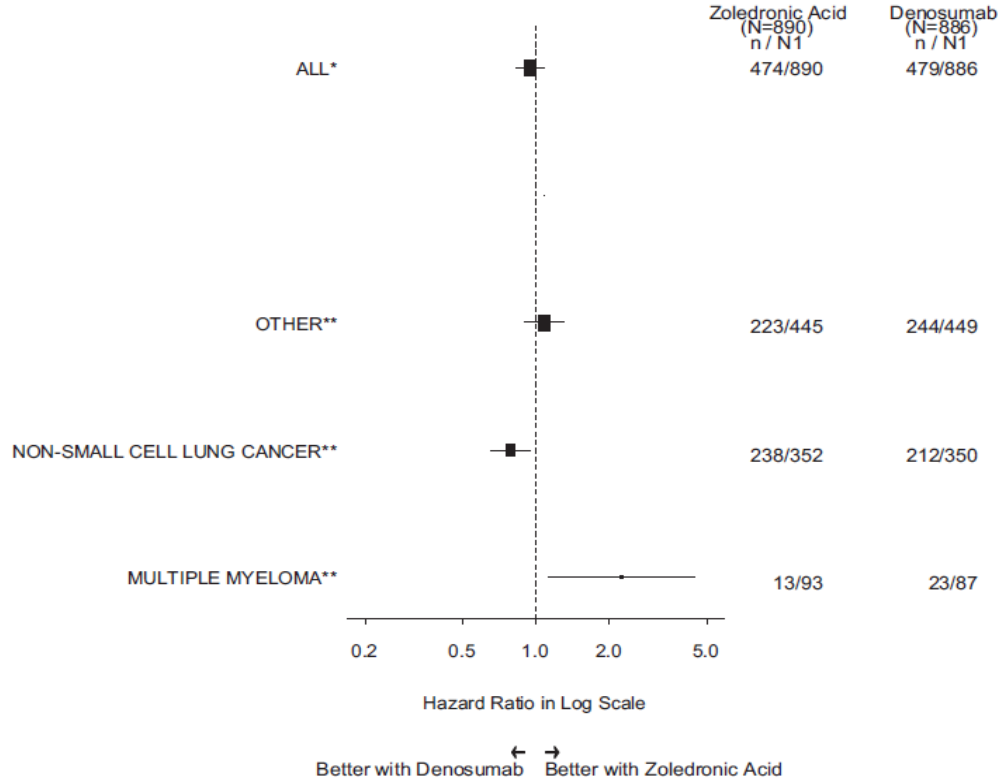
N = Number of subjects randomized
N1 = Number of subjects in each tumor type; n = Number of subjects with SRE; NE = Not estimatable
Hazard Ratio and 95% CI based on a Cox proportional regression model stratified by previous SRE and systemic anti-cancer
Include tumor types with a total number of subjects > 10

Table 18. Secondary efficacy endpoints by Tumour Type

Endpoint	Denosumab vs Zoledronic Acid Hazard Ratio or Rate Ratio [a]							
	Breast Cancer (Study 20050136) (N = 2046)		Prostate Cancer (Study 20050103) (N = 1901)		Other Solid Tumors (Study 20050244) (N = 1597)		Multiple Myeloma (Study 20050244) (N = 179)	
	Pt Est (95% CI)	p-value	Pt Est (95% CI)	p-value	Pt Est (95% CI)	p-value	Pt Est (95% CI)	p-value
Time to first on-study SRE (superiority)[b]	0.82 (0.71, 0.95)	0.0101	0.82 (0.71, 0.95)	0.0085	0.81 (0.68, 0.96)	0.0168	1.03 (0.68, 1.57)	0.8911
Time to first-and-subsequent SRE[c]	0.77 (0.66, 0.89)	0.0006	0.82 (0.71, 0.94)	0.0044	0.85 (0.72, 1.00)	0.0479	1.21 (0.86, 1.71)	0.2753

N = Number of subjects randomized
[a] Hazard ratio or rate ratio< 1 favors denosumab.
[b] Hazard ratio relative to zoledronic acid based on the Cox proportional hazards model with treatment groups as the independent variable and stratified by study (for overall only) and the randomized stratification factors.
[c] Rate ratio relative to zoledronic acid based on the Andersen-Gill model stratified by the randomization stratification factors.

Figure 23. Forest Plot of Overall Survival by Tumour Type for Study 2005-0244 (Post hoc)



N = Number of subjects randomized
N1 = Number of subjects in each tumor type by actual strata; n = Number of deaths;
*** Hazard Ratio and 95% CI based on a Cox proportional regression model stratified by Stratification factors**
**** Hazard Ratio and 95% CI based on a Cox proportional regression model stratified by previous SRE and systemic anti-cancer therapy**

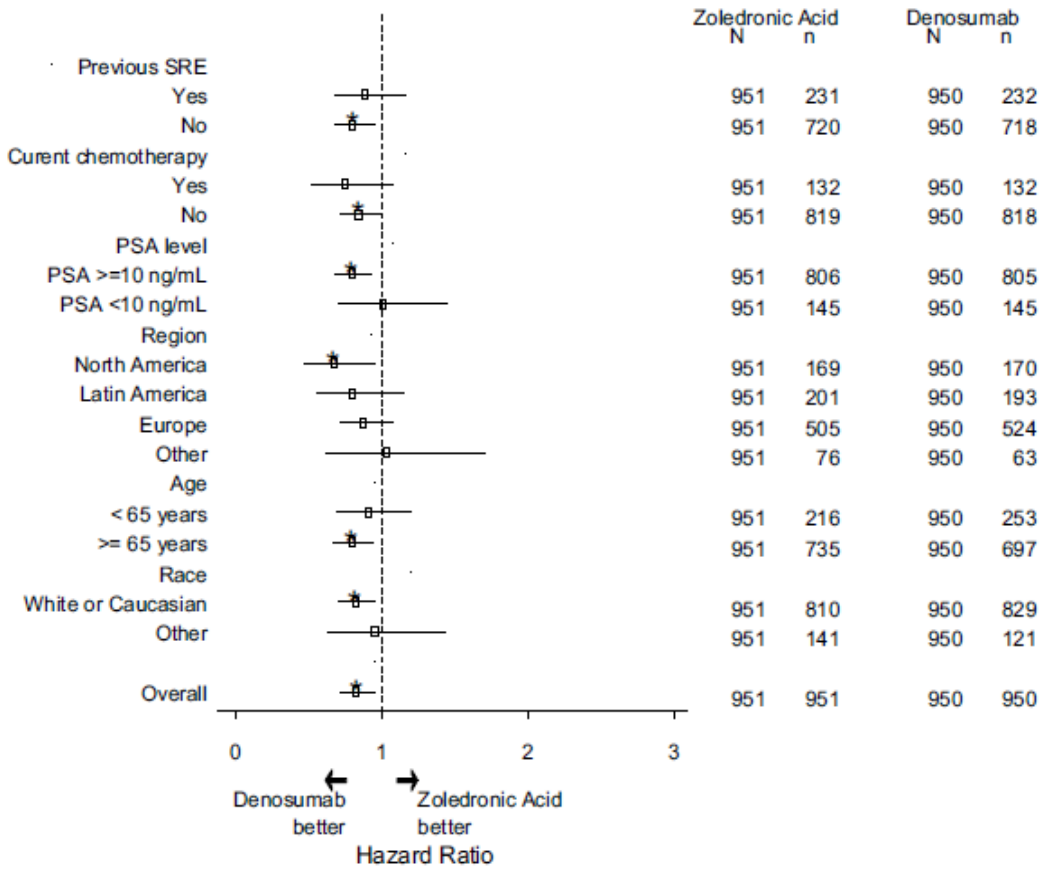
Other Subgroup Analyses in Pivotal Trials

Pre specified subgroup analyses by factors such as age, geographical region, race, gender, disease markers and concurrent treatments were performed in each of the three pivotal studies. These analyses are summarised by way of Forest plots in Figures 21, 24 and 25. In general, a treatment effect was consistent across the spectrum of subgroup analyses with the notable exceptions listed below:

- *Study 2005-0103. H*azard ratios across the spectrum of subgroups were < 1 except for two subgroups (PSA<10 ng/mL and 'other' geographical region). Both these subgroups had small subject numbers and wide confidence intervals and are unlikely to be of clinical significance.
- *Study 2005*-0136. Quantitative differences in treatment effect were noted for race (HR 0.90 for White subjects and 0.53 for Non-White) and age. Given the mix of races included in the 'Non-White' subgroup, drawing conclusions regarding racial differences in treatment effect is difficult. Time to first on study SRE was longer for zoledronic acid than for placebo in subjects < 50 years of age. This effect was significantly different from that in subjects > 50 years of age when tested quantitatively, but not qualitatively (Gail and Simon test). This suggests that the magnitude of the effect may be different across age groups but no evidence of difference in the direction of the effect exists.
- *Study 2005-0244*. In addition to the MM subgroup (discussed above), 'Other' geographical region, 'Other' race (Non-White) and female gender all had HR > 1. Confidence intervals for these subgroups all crossed 1. Once again, given the heterogeneous nature of the two 'Other' subgroups makes it difficult to draw any

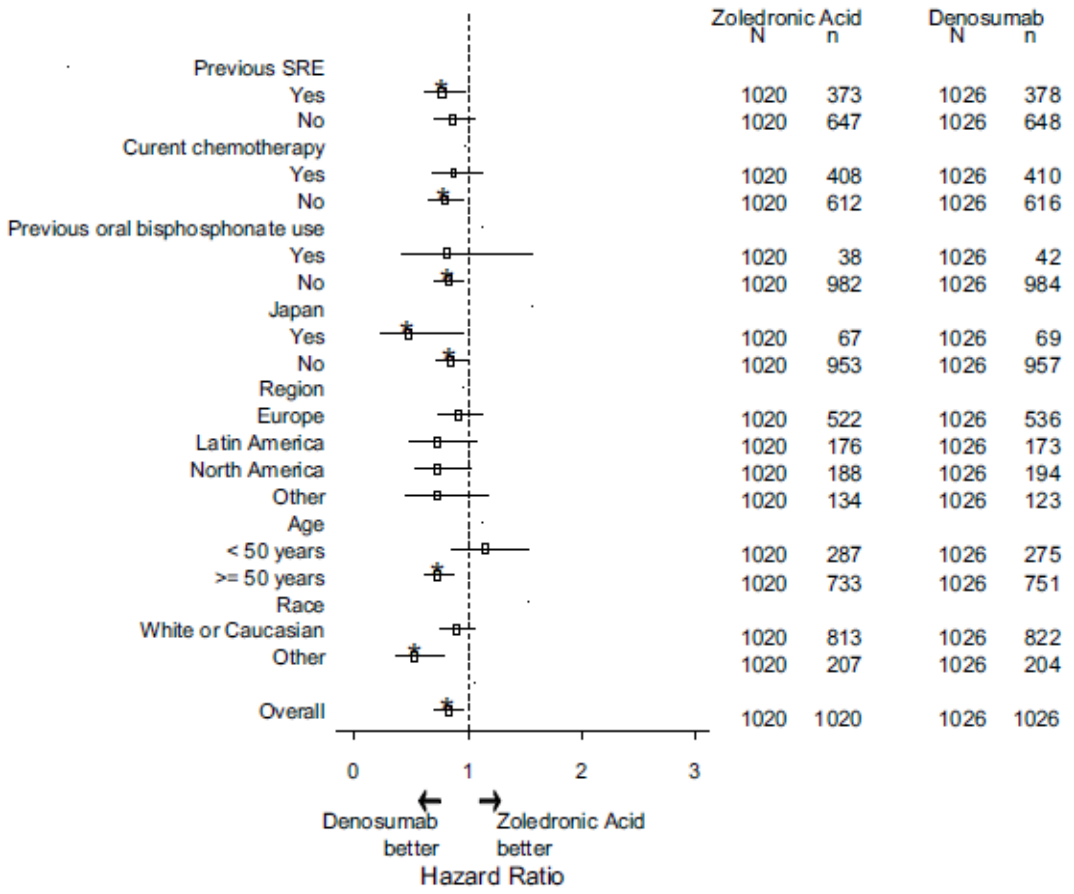
definitive conclusions about these results. The HR for female gender was close to 1, with the confidence interval overlapping the majority of the confidence interval of male gender and is therefore unlikely to be of significance.

Figure 24. Forest Plot of Time to First on study SRE by Subgroup for Study 2005-0103



Hazard ratio and 95% CI from a Cox proportional hazards model stratified by the randomization stratification variables
*** indicates significance at a 5.0% nominal level**

Figure 25. Forest Plot of Time to First on study SRE by Subgroup for Study 2005-0136



Hazard ratio and 95% CI from a Cox proportional hazards model stratified by the randomization stratification variables.

Clinical studies in special populations

No clinical studies have been designed specifically to assess special populations. In particular, no paediatric studies have been performed. However, it is noted in the current Australian submission that the FDA has requested a series of paediatric trials to be performed as part of their subsequent licensing requirements. Geriatric subjects were included in the three pivotal studies (see Table 19, Figures 21 and 24-25 and discussion above in ancillary analysis). Subjects with significant renal impairment (creatinine clearance (CrCl) < 30mL/min) and hepatic impairment (defined by serum bilirubin and transaminase cut off values which are not true reflections of hepatic function) where specifically excluded from the clinical trials.

Table 19. Geriatric Aged Subjects Included in the Pivotal Trials.

Study ID	Mean Age	Age Range	% Age ≥ 65	% Age ≥ 75
2005-0103	70.8	38, 91	75.3	36.0
2005-0136	56.7	24, 91	26.4	6.1
2005-0244	59.9	18, 89	35.8	8.3

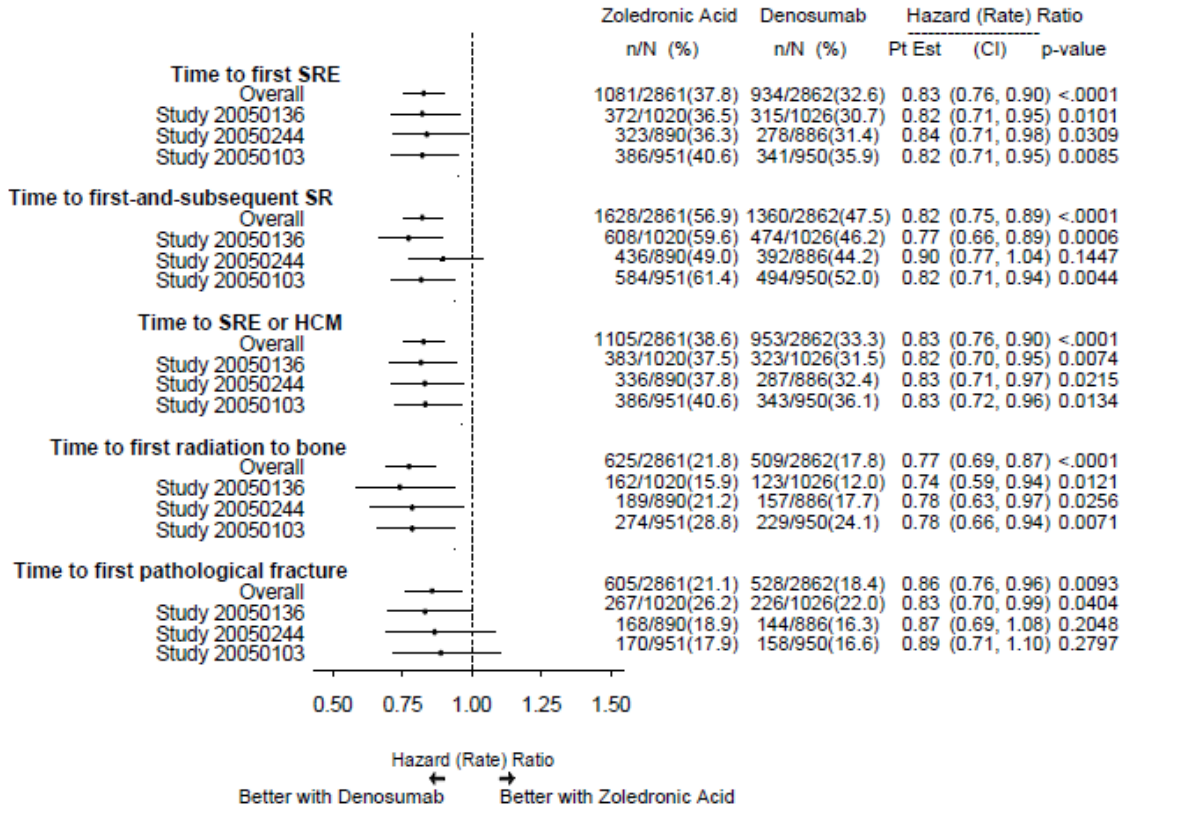
Analysis performed across trials (pooled analyses and meta-analysis)

An integrated analysis of the efficacy results from the three pivotal trials was conducted. Each of the trials shared common study design, endpoints and statistical methodology. Baseline characteristics and subject disposition are outlined in Tables 10, 12 and 13 above.

In the integrated analysis, denosumab was found to be superior to zoledronic acid for first on study SRE (HR 0.83, 95% CI 0.76-0.90, p<0.0001) and time to first and subsequent on study SRE (HR 0.82, 95% CI 0.75-0.89, p<0.0001). The integrated analysis also found significant superiority of denosumab for the two most common components of the composite SRE endpoint: risk of radiation to bone (HR 0.77, 95% CI 0.69-0.87, p<0.0001) and pathological fracture (HR 0.86, 95% CI 0.76-0.96, p=0.0093). Homogeneity testing did not find inconsistent effect across the four components of the SRE endpoint (p>0.478). A Forest plot of the efficacy endpoints is found in Figure 26. Nonetheless, the overall survival and disease progression (overall and bone specific) following denosumab treatment were not significantly different from that of patients given zoledronic acid (see Table 20).

Subgroup analysis for age, gender, race, geographic region, previous SRE, osteolytic or osteoblastic bone lesion was conducted on the integrated analysis. A Forest plot of the results of this analysis on the primary efficacy endpoint is shown in Figure 27. No significant effect on efficacy was seen for any of the subgroups except for a quantitative difference for both the osteolytic and osteoblastic lesion subgroups, with pure osteolytic lesions responding less well than non-osteolytic lesions (HR 0.99 and 0.79) and pure osteoblastic lesions responding better than non-osteoblastic lesions (HR 0.71 and 0.90). Subgroup analysis of time to first and subsequent on study SRE was similar, with only the osteolytic bone lesion type having any significant difference in treatment response (rate ratios 0.98 and 0.78 for the pure osteolytic and non-osteolytic subgroups, respectively).

Figure 26. Forest Plot of Integrated Analysis Results of Efficacy Endpoints



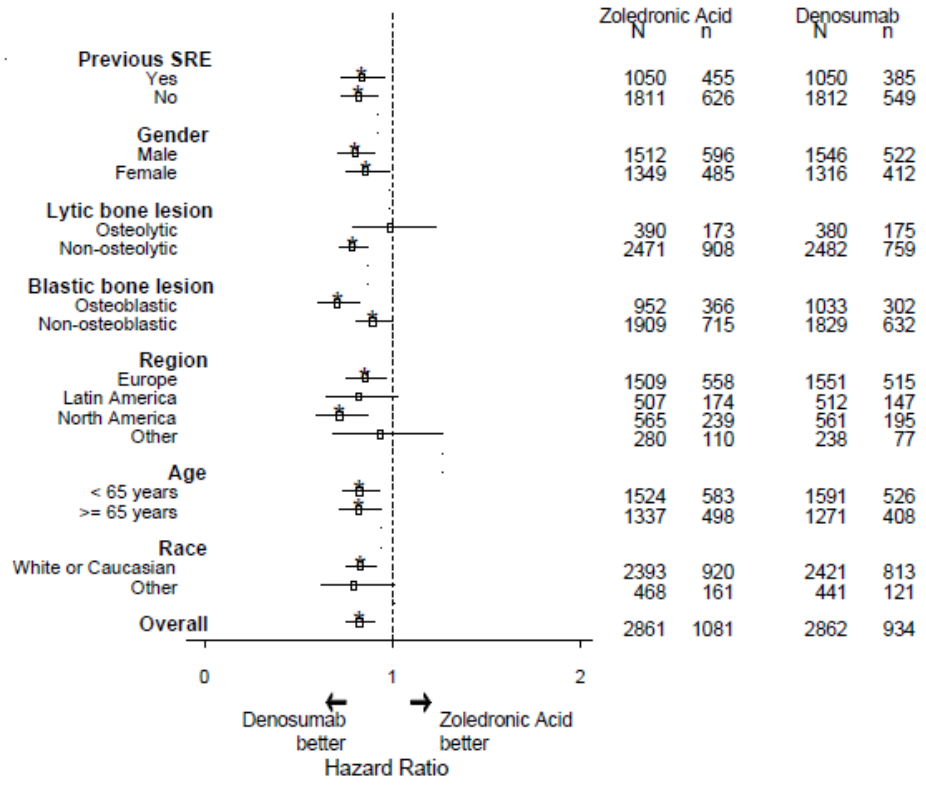
N = Number of subjects randomized
n = Number of subjects with events except for time to first-and-subsequent SRE; number of events for time to first-and-subsequent SRE
Hazard ratio estimate and p-value based on a Cox proportional hazards model stratified by study and randomization stratification variables.
Rate ratio estimate and p-value based on an Andersen-Gill model stratified by study and randomization stratification variables

Table 20. Integrated Analysis of Disease Related Endpoints

Endpoint	Denosumab vs Zoledronic Acid Hazard Ratio[a]							
	Study 20050136		Study 20050244		Study 20050103		Overall	
	Pt Est (95% CI)	p-value	Pt Est (95% CI)	p-value	Pt Est (95% CI)	p-value	Pt Est (95% CI)	p-value
Overall survival	0.95 (0.81, 1.11)	0.4921	0.95 (0.83, 1.08)	0.4305	1.03 (0.91, 1.17)	0.6511	0.99 (0.91, 1.07)	0.7120
Time to disease progression excluding death	1.00 (0.89, 1.11)	0.9302	1.00 (0.89, 1.12)	0.9979	1.06 (0.95, 1.18)	0.3000	1.02 (0.95, 1.08)	0.6328
Time to overall disease progression or death (any cause)	1.00 (0.90, 1.11)	0.9551	1.01 (0.91, 1.13)	0.8499	1.05 (0.95, 1.16)	0.3542	1.02 (0.96, 1.08)	0.5456
Time to disease progression in bone	0.99 (0.87, 1.13)	0.8674	0.98 (0.83, 1.16)	0.8188	0.92 (0.80, 1.06)	0.2629	0.96 (0.88, 1.04)	0.2913

[a] For overall survival, disease progression, and disease progression in bone: Based on Cox proportional hazards model with treatment groups, age, time from initial diagnosis of primary cancer to first evidence of metastasis, time from initial diagnosis of primary cancer to first bone metastasis, visceral metastasis, hormone receptor status (136/overall only), Her-2 status (136/overall only), prior adjuvant treatment (136/overall only), postmenopausal status (136/overall only), baseline ECOG, and gender (244/overall only) (plus type of bone lesion at baseline, ethnic group/race , and previous oral bisphosphonate use [103 only] for disease progression in bone only) as the independent variable and stratified by study (overall only) and the randomization stratification factors. Hazard ratio < 1 favors denosumab.

Figure 27. Forest Plot of Time to First on study SRE by Subgroup for Integrated Analysis



N = Number of subjects randomized; n = number of subjects with events.
Hazard ratio and 95% CI from a Cox proportional hazards model stratified by study and randomization stratification variables.
* represents p-value < 0.05.

Supportive studies

Results collected from the two extended blinded treatment phase periods of Studies 2005-0136 and 2005-0244 were reported separately from the pivotal trial results in the sponsor's submission.

Study 2005-0136 DBE was an extended double blinded treatment phase of Study 2005-0136. The full study period reported was from 27 April 2006 until 20 July 2009. Enrolment criteria and study design was as per the primary treatment phase. Subject flow and withdrawals are summarised in Table 21. Efficacy outcomes are summarised in Table 22 and do not differ significantly from that of the primary analysis.

Table 21. Summary of Subject Withdrawals for Study 2005-0136. Blinded Treatment Extension.

	Zoledronic Acid 4 mg Q4W n (%)	Denosumab 120 mg Q4W n (%)	All n (%)
Randomized	1020	1026	2046
On study through blinded treatment cutoff date	386 (37.8)	366 (35.7)	752 (36.8)
Discontinued prior to blinded treatment cutoff date	634 (62.2)	660 (64.3)	1294 (63.2)
Death	193 (18.9)	196 (19.1)	389 (19.0)
Disease progression	141 (13.8)	151 (14.7)	292 (14.3)
Consent withdrawn[a]	134 (13.1)	142 (13.8)	276 (13.5)
Subject request[b]	68 (6.7)	78 (7.6)	146 (7.1)
Adverse event	47 (4.6)	31 (3.0)	78 (3.8)
Other	20 (2.0)	21 (2.0)	41 (2.0)
Administrative decision	17 (1.7)	16 (1.6)	33 (1.6)
Noncompliance	5 (0.5)	12 (1.2)	17 (0.8)
Lost to follow-up	7 (0.7)	10 (1.0)	17 (0.8)
Ineligibility determined	2 (0.2)	2 (0.2)	4 (0.2)
Protocol deviation	0 (0.0)	1 (<0.1)	1 (<0.1)

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Percentages based on number of subjects randomized
[a] Subject withdrew full consent to participate in study any longer, including long-term follow-up
[b] Subject does not wish to attend any further Q4W assessments but agrees to be contacted for survival follow-up

Table 22. Summary of Efficacy Outcomes for Study 2005-0136. Blinded Treatment Extension.

Endpoint	Denosumab vs Zoledronic Acid Hazard Ratio or Rate Ratio[a] (Primary Analysis Results)[b]				Denosumab vs Zoledronic Acid Hazard Ratio or Rate Ratio[a] (Blinded Treatment Analysis Results)[c]			
	Pt Est	(95% CI)	p-value (unadjusted)	p-value (adjusted)	Pt Est	(95% CI)	p-value (unadjusted)	p-value (adjusted)
Time to first on-study SRE (noninferiority)	0.82	(0.71, 0.95)	< 0.0001	< 0.0001	0.82	(0.71, 0.95)	< 0.0001	< 0.0001
Time to first on-study SRE (superiority)	0.82	(0.71, 0.95)	0.0101	0.0101	0.82	(0.71, 0.95)	0.0096	0.0096
Time to first and subsequent on-study SRE	0.77	(0.66, 0.89)	0.0006	0.0012	0.78	(0.68, 0.90)	0.0008	0.0016
Time to first on-study SRE or HCM	0.82	(0.70, 0.95)	0.0074		0.82	(0.71, 0.95)	0.0076	
Time to radiation in bone	0.74	(0.59, 0.94)	0.0121		0.76	(0.61, 0.96)	0.0184	
Overall survival	0.95	(0.81, 1.11)	0.4921		0.96	(0.83, 1.11)	0.5605	
Time to disease progression in bone	0.99	(0.87, 1.13)	0.8674		1.00	(0.87, 1.13)	0.9523	
Time to overall disease progression	1.00	(0.89, 1.11)	0.9302		0.98	(0.88, 1.09)	0.7295	
Time to overall disease progression or death (any cause)	1.00	(0.90, 1.11)	0.9551		0.99	(0.89, 1.09)	0.7788	
Time to first symptomatic SRE	0.76	(0.61, 0.93)	0.0092		0.79	(0.64, 0.96)	0.0194	

HCM = hypercalcemia of malignancy; SRE = skeletal-related event
[a] Hazard ratio or rate ratio < 1 favors denosumab
[b] Primary analysis through 06 March 2009
[c] Entire blinded treatment analysis through 20 July 2009

Study 2005-0244 DBE was an extended blinded treatment phase of Study 2005-0244. The entire study period ran from 21 June 2006 until 21 October 2009. Enrolment criteria and study design was as per the primary treatment phase. Subject flow and withdrawals are summarised in Table 23. Efficacy outcomes are summarised in Table 24 and again did not differ significantly from that of the primary analysis.

Table 23. Summary of Subject Withdrawals for Study2005-0244. Blinded Treatment Extension.

	Zoledronic Acid 4 mg Q4W n (%)	Denosumab 120 mg Q4W n (%)	All n (%)
Randomized	890	886	1776
Completed study[a]	128 (14.4)	123 (13.9)	251 (14.1)
Discontinued prior to study ended	762 (85.6)	763 (86.1)	1525 (85.9)
Death	330 (37.1)	324 (36.6)	654 (36.8)
Disease progression	116 (13.0)	144 (16.3)	260 (14.6)
Consent withdrawn[b]	148 (16.6)	134 (15.1)	282 (15.9)
Other	38 (4.3)	47 (5.3)	85 (4.8)
Adverse event	58 (6.5)	41 (4.6)	99 (5.6)
Subject request[c]	36 (4.0)	25 (2.8)	61 (3.4)
Lost to follow-up	17 (1.9)	23 (2.6)	40 (2.3)
Noncompliance	13 (1.5)	18 (2.0)	31 (1.7)
Administrative decision	4 (0.4)	4 (0.5)	8 (0.5)
Protocol deviation	0 (0.0)	2 (0.2)	2 (0.1)
Ineligibility determined	2 (0.2)	1 (0.1)	3 (0.2)

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Percentages based on number of subjects randomized
[a] Continued on study until study ended
[b] Subject withdrew full consent to participate in study any longer, including long term follow-up
[c] Subject does not wish to attend any further Q4W assessments, but agrees to be contacted for survival follow-up

Table 24. Summary of Efficacy Outcomes for Study 2005-0244. Blinded-Treatment Extension.

Endpoint	Denosumab vs Zoledronic Acid Hazard Ratio or Rate Ratio[a] (Primary Analysis Results)[b]				Denosumab vs Zoledronic Acid Hazard Ratio or Rate Ratio[a] (Blinded Treatment Analysis Results)[c]			
	Pt Est	(95% CI)	p-value (unadjusted)	p-value (adjusted)	Pt Est	(95% CI)	p-value (unadjusted)	p-value (adjusted)
Time to first on-study SRE (noninferiority)	0.84	(0.71, 0.98)	0.0007	0.0007	0.84	(0.71, 0.98)	0.0006	0.0006
Time to first on-study SRE (superiority)	0.84	(0.71, 0.98)	0.0309	0.0619	0.84	(0.71, 0.98)	0.0300	0.0600
Time to first and subsequent on-study SRE	0.90	(0.77, 1.04)	0.1447	0.1447	0.88	(0.76, 1.01)	0.0779	0.0779
Time to radiation in bone	0.78	(0.63, 0.97)	0.0256		0.79	(0.64, 0.98)	0.0291	
Time to first on-study SRE or HCM	0.83	(0.71, 0.97)	0.0215		0.83	(0.71, 0.97)	0.0205	
Overall survival	0.95	(0.83, 1.08)	0.4305		0.94	(0.83, 1.06)	0.2877	
Time to overall disease progression	1.00	(0.89, 1.12)	0.9979		1.01	(0.90, 1.13)	0.9175	
Time to overall disease progression or death (any cause)	1.01	(0.91, 1.13)	0.8499		1.01	(0.91, 1.12)	0.8523	
Time to disease progression in bone	0.98	(0.83, 1.16)	0.8188		0.98	(0.83, 1.15)	0.7881	
Time to first symptomatic SRE	0.84	(0.69, 1.02)	0.0738		0.84	(0.70, 1.02)	0.0748	

HCM = hypercalcemia of malignancy; SRE = skeletal-related event
[a] Hazard ratio or rate ratio < 1 favors denosumab
[b] Primary analysis through 30 April 2009
[c] Entire blinded treatment analysis through 21 October 2009

Evaluator's overall conclusions on clinical efficacy

The sponsor provided the efficacy data from three pivotal, randomized, multicentre, double blinded, active controlled clinical trials in support of the efficacy of denosumab for

treating adult patients with advanced cancer involving bone. Supportive data is supplied by the controlled, dose ranging, Phase II studies. In general, the studies were of adequate design with a clear and appropriate plan of analysis. All three of the controlled studies assessed subjects for up to 30 months, which is an adequate duration to evaluate short to medium term outcomes.

The primary efficacy endpoint in the Phase III studies was the composite outcome of SRE which encompasses fractures, radiation or surgery to bone, and spinal cord compression due to cancer. Supportive secondary analyses including evaluation of the components of the SRE, time to first and subsequent SRE, overall survival and disease progression. All of the efficacy endpoints examined have clinical utility. The efficacy endpoints (primary and major secondary) utilised in the Phase III studies was discussed with the FDA and addresses the indications being sought for by the sponsor in the current Australian application. The primary efficacy analysis was a non inferiority comparison with the current approved standard of care therapy (IV zoledronic acid 4 mg every 4 weeks), and the secondary analyses included a superiority comparison for selected relevant endpoints.

The key efficacy conclusions provided by the three pivotal studies were:

- In each of the Phase III studies, denosumab achieved the primary efficacy endpoint of non inferiority with respect to time to first SRE compared to zoledronic acid;
- In the secondary superiority analysis of time to first SRE, denosumab was statistically superior to zoledronic acid in reducing the risk of developing another SRE in all of the three pivotal studies;
- For two of the pivotal three studies (breast and prostate cancer), time to radiation of bone and time to first symptomatic SRE were also in favour of denosumab therapy rather than zoledronic acid treatment;
- None of the pivotal trials demonstrated a significant difference between denosumab and zoledronic acid for overall survival and disease progression (overall and bone specific);
- The composite endpoint of either first on study SRE or hypercalcaemia of malignancy was principally explained by SRE (as the absolute number of HCM events was very small) and as such, no claim of specifically treating HCM could be claimed by the current dataset;
- Subgroup analysis of tumour type for Study 2005-0244 showed an inferior survival for myeloma patients treated with denosumab compared with those who received zoledronic acid. Further analysis of this study also suggested that the rates of response to denosumab may be lower in subjects of non-Caucasian ethnicity or females compared with that of zoledronic acid but the absolute difference in numbers in these subgroup analyses is small and therefore made it difficult to draw definitive conclusions. [25]

In summary, the efficacy results of the Phase III clinical trial program indicate a consistent response to denosumab treatment with a modest clinical effect (prevention of further SRE but little change to overall survival or disease progression).

[25] The sponsor wishes to clarify that the clinical evaluator's reference to apparent differences in treatment effect for gender and ethnicity in Study 20050244 are based on subgroup analysis of this single study. The sponsor considers that the more appropriate dataset to draw conclusions on subgroups from is the combined 3 study dataset where small numbers are less likely to limit interpretations. In the combined analysis the apparent differences observed by the clinical evaluator in Study 20050244 are no longer evident and instead move in a favourable direction.

Safety

Introduction

The denosumab clinical development program pertaining to the indication of prevention of SRE in adult patients with malignancy involving bone comprises eight clinical studies in total. All were conducted in the period between September 2001 and October 2009. Three of these studies were long-term Phase III trials (Studies 2005-0136, 2005-0103 and 2005-0244) and these form the pivotal basis for the safety evaluation. A further two dose ranging studies (2004-0113 and 2004-0114) also contributed safety data in support of the current Australian application. In addition, the complete or interim safety data from a further three studies (2005-0147, 2005-0134 and 2004-0215) in adult subjects with cancer (but with different treatment indications than requested by the sponsor in this submission such as giant cell tumour, multiple myeloma and primary prevention of SRE in prostate cancer) have also been provided. Previous studies involving healthy subjects and those with post menopausal osteoporosis have been evaluated with the initial licensing application in Australia.

Patient exposure

A summary of patient exposure to denosumab is outlined in Table 25. Of most relevance to the current evaluation is the subset of subjects recruited into the advanced cancer studies, which comprises the majority of the subject exposure to total dataset. This malignancy treatment subset comprises the three pivotal Phase III trials including the extended double blind treatment phase (as described in the *Efficacy* section). In this cohort, a total of 2151 subjects were continuously exposed to denosumab for a period of at least 6 months, with 1535 subjects being exposed for more than 1 year. The subjects included in this cohort are generally similar to those of the proposed marketing indication. Furthermore, most of those subjects were exposed to denosumab at the dosage regimen proposed by the sponsor in this application. All of the pivotal trials were active controlled with the comparator product zoledronic acid 4mg IV fourth weekly.

The *Primary Advanced Cancer Safety Analysis Set* included all subjects who received one or more doses of investigational drug from the primary blinded treatment phases of the three pivotal trials. The *Primary Advanced Randomised Analysis Set* included all subjects randomised in the three trials.

The individual studies in this subset are as follows:

- *Study 2005-0103* included 951 men in the denosumab treatment arm. The study included subjects with prostate cancer and with a mean age of 70.8 years. Of the denosumab treated patients, 50.2% received denosumab for a period of at least 12 months.
- *Study 2005-0136* included 1026 subjects in the denosumab group. The study included subjects with breast cancer (almost exclusively women) and with a mean age of 56.7 years. Of the denosumab treated patients, 66.8% received denosumab for a period of at least 12 months.
- *Study 2005-0244* included 889 subjects in the denosumab arm. The study included subjects with a heterogeneous mix of advanced cancers (not prostate or breast cancer), with a mean age of 60 years and a predominance of males (65%). Of the denosumab treated patients, 55.3% were exposed for more than 6 months and 30.8% were exposed for more than one year. Included in the denosumab group were 350 subjects with non small cell lung cancer, 87 subjects with multiple myeloma and 445 subjects with a variety of other solid tumours. The number of subjects with each individual cancer type were typically small, with the largest

"Other cancer" groups being renal (n=70 in the denosumab arm), colon/rectal (n=55) and small cell lung (n=61).

Exposure breakdown by age, sex, race and renal impairment is provided in Table 26. Subjects with a creatinine clearance (by Cockcroft-Gault) of less than 30 mL/min were excluded from the Phase III trials.

The dataset provides adequate long-term exposure data, particularly for the indications of prostate cancer and breast cancer. However, data for other tumours types is limited and was therefore analysed collectively. Of particular importance is multiple myeloma patient subset as the disease mechanism (primary lytic bone lesions rather than metastatic deposits) is biologically distinct from the other types of cancers being studied.

Table 25. Summary of Subject Exposure to Denosumab for Safety Evaluation

	Denosumab					
	≥ 1 Dose	≥ 1 Month	≥ 6 Months	≥ 1 Year	≥ 2 Years	≥ 3 Years
Overall total exposure	3904	3870	2526	1729	540	10
Phase 1 studies[a]	647	645	75	0	0	0
Phase 2 supportive studies[b]	284	279	238	169	0	0
Phase 3 advanced cancer studies[c]	2841	2814	2151	1535	540	10
Phase 2 studies in other indications[d]	132	132	62	25	0	0

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Data included in this analysis are the same as that used for the primary analysis CSRs included in this marketing application, with the exception of Studies 20050136 and 20050244, for which data are included up to end of study date or entire blinded treatment cutoff date, whichever occurred first

[a] Includes studies 20010123, 20010124, 20030148, 20030164, 20030180, 20040176, 20040245, 20050227, 20060286, and 20060446

[b] Includes studies 20040113 and 20040114

[c] Includes studies 20050136, 20050244 and 20050103

[d] Includes studies 20050134 and 20040215

Table 26. Summary of Subject Exposure to Denosumab by Baseline Characteristics

	Number of Subjects		**Total Subject-Years**	
	Male	**Female**	**Male**	**Female**
Total Primary Safety Analysis Set	1535	1306	1508.1	1588.2
By Age				
· Aged < 65 years	634	947	579.9	1159.1
· Aged ≥ 65 years	901	359	910.2	429.1
· Aged < 75 years	1148	1221	1133.4	1495.9
· Aged ≥ 75 years	387	85	374.7	92.4
	Both Sexes		**Both Sexes**	
By Ethnicity				
· White/Caucasian	2404		2633.7	
· Black/African American	83		86.1	
· Hispanic/Latino	153		154.3	
· Asian	89		75.5	
· Japanese	72		101.4	
By Renal Impairment				
· ≤ 60mL/min	496		465.9	
· >60mL/min	2326		2609.3	

Adverse events

Pivotal Phase III Studies

As expected in a population suffering cancer, most subjects in the Primary Advanced Cancer Safety Analysis Set had at least one adverse event (AE). The overall incidence of AEs was similar between the two treatment groups (96.2% for denosumab and 96.8% for zoledronic acid). The most common AEs in each arm across the three pivotal studies are summarised in Table 27. Most AEs occurred at a similar event rate between the two treatment groups. An imbalance in crude incidence exists for AEs that could be collectively attributed to zoledronic acid infusion reactions; for example, pyrexia (19.8% for zoledronic acid versus 14.4% for denosumab), arthralgia (22.3% for zoledronic acid versus 20.1% for denosumab) and bone pain (22.5% for zoledronic acid compared with 19.9% for denosumab). The incidence of hypocalcaemia was more common in the denosumab groups (9.3% for denosumab versus 4.7% for zoledronic acid). A modest imbalance in incidence (favouring zoledronic acid) is also seen for dyspnoea (20.6% for denosumab compared with 17.9% for zoledronic acid) and diarrhoea (20.3% for denosumab versus 18.7% for zoledronic acid).

Table 27. Common Adverse Events by Preferred Term from the Pivotal Phase III Studies (≥5% incidence in either treatment group). Table continued across two pages.

	Study 20050136		Study 20050244		Study 20050103		Overall	
Preferred Term	Zoledronic Acid 4 mg Q4W (N=1013) n (%)	Denosumab 120 mg Q4W (N=1020) n (%)	Zoledronic Acid 4 mg Q4W (N=878) n (%)	Denosumab 120 mg Q4W (N=878) n (%)	Zoledronic Acid 4 mg Q4W (N=945) n (%)	Denosumab 120 mg Q4W (N=943) n (%)	Zoledronic Acid 4 mg Q4W (N=2836) n (%)	Denosumab 120 mg Q4W (N=2841) n (%)
Number of subjects reporting adverse events[a]	985 (97.2)	977 (95.8)	842 (95.9)	841 (95.8)	918 (97.1)	916 (97.1)	2745 (96.8)	2734 (96.2)
Nausea	384 (37.9)	356 (34.9)	266 (30.3)	248 (28.2)	245 (25.9)	272 (28.8)	895 (31.6)	876 (30.8)
Anaemia	232 (22.9)	192 (18.8)	286 (32.6)	242 (27.6)	341 (36.1)	337 (35.7)	859 (30.3)	771 (27.1)
Fatigue	324 (32.0)	301 (29.5)	220 (25.1)	211 (24.0)	222 (23.5)	257 (27.3)	766 (27.0)	769 (27.1)
Back pain	264 (26.1)	241 (23.6)	196 (22.3)	173 (19.7)	287 (30.4)	304 (32.2)	747 (26.3)	718 (25.3)
Decreased appetite	192 (19.0)	193 (18.9)	228 (26.0)	196 (22.3)	274 (29.0)	267 (28.3)	694 (24.5)	656 (23.1)
Asthenia	202 (19.9)	196 (19.2)	180 (20.5)	172 (19.6)	239 (25.3)	239 (25.3)	621 (21.9)	607 (21.4)
Constipation	205 (20.2)	176 (17.3)	214 (24.4)	191 (21.8)	251 (26.6)	236 (25.0)	670 (23.6)	603 (21.2)
Dyspnoea	190 (18.8)	222 (21.8)	200 (22.8)	220 (25.1)	117 (12.4)	143 (15.2)	507 (17.9)	585 (20.6)
Diarrhoea	207 (20.4)	231 (22.6)	171 (19.5)	168 (19.1)	152 (16.1)	178 (18.9)	530 (18.7)	577 (20.3)
Arthralgia	291 (28.7)	250 (24.5)	139 (15.8)	126 (14.4)	202 (21.4)	194 (20.6)	632 (22.3)	570 (20.1)
Vomiting	238 (23.5)	212 (20.8)	183 (20.8)	186 (21.2)	149 (15.8)	168 (17.8)	570 (20.1)	566 (19.9)

	Study 20050136		Study 20050244		Study 20050103		Overall	
Preferred Term	Zoledronic Acid 4 mg Q4W (N=1013) n (%)	Denosumab 120 mg Q4W (N=1020) n (%)	Zoledronic Acid 4 mg Q4W (N=878) n (%)	Denosumab 120 mg Q4W (N=878) n (%)	Zoledronic Acid 4 mg Q4W (N=945) n (%)	Denosumab 120 mg Q4W (N=943) n (%)	Zoledronic Acid 4 mg Q4W (N=2836) n (%)	Denosumab 120 mg Q4W (N=2841) n (%)
Bone pain	238 (23.5)	186 (18.2)	156 (17.8)	143 (16.3)	245 (25.9)	235 (24.9)	639 (22.5)	564 (19.9)
Pain in extremity	222 (21.9)	204 (20.0)	132 (15.0)	123 (14.0)	196 (20.7)	197 (20.9)	550 (19.4)	524 (18.4)
Oedema peripheral	150 (14.8)	174 (17.1)	138 (15.7)	106 (12.1)	174 (18.4)	192 (20.4)	462 (16.3)	472 (16.6)
Cough	180 (17.8)	171 (16.8)	156 (17.8)	173 (19.7)	83 (8.8)	93 (9.9)	419 (14.8)	437 (15.4)
Pyrexia	247 (24.4)	170 (16.7)	182 (20.7)	139 (15.8)	133 (14.1)	100 (10.6)	562 (19.8)	409 (14.4)
Headache	214 (21.1)	197 (19.3)	96 (10.9)	101 (11.5)	72 (7.6)	62 (6.6)	382 (13.5)	360 (12.7)
Musculoskeletal pain	148 (14.6)	149 (14.6)	99 (11.3)	97 (11.0)	138 (14.6)	111 (11.8)	385 (13.6)	357 (12.6)
Weight decreased	94 (9.3)	79 (7.7)	106 (12.1)	100 (11.4)	132 (14.0)	151 (16.0)	332 (11.7)	330 (11.6)
Insomnia	136 (13.4)	124 (12.2)	94 (10.7)	89 (10.1)	94 (9.9)	89 (9.4)	324 (11.4)	302 (10.6)
Abdominal pain	119 (11.7)	122 (12.0)	97 (11.0)	96 (10.9)	64 (6.8)	74 (7.8)	280 (9.9)	292 (10.3)
Neutropenia	123 (12.1)	125 (12.3)	109 (12.4)	99 (11.3)	46 (4.9)	53 (5.6)	278 (9.8)	277 (9.8)
Alopecia	142 (14.0)	159 (15.6)	62 (7.1)	48 (5.5)	62 (6.6)	58 (6.2)	266 (9.4)	265 (9.3)
Hypocalcaemia	34 (3.4)	56 (5.5)	49 (5.6)	93 (10.6)	51 (5.4)	116 (12.3)	134 (4.7)	265 (9.3)
Chest pain	84 (8.3)	93 (9.1)	93 (10.6)	97 (11.0)	70 (7.4)	73 (7.7)	247 (8.7)	263 (9.3)
Dizziness	114 (11.3)	106 (10.4)	75 (8.5)	70 (8.0)	65 (6.9)	56 (5.9)	254 (9.0)	232 (8.2)

	Study 20050136		Study 20050244		Study 20050103		Overall	
Preferred Term	Zoledronic Acid 4 mg Q4W (N=1013) n (%)	Denosumab 120 mg Q4W (N=1020) n (%)	Zoledronic Acid 4 mg Q4W (N=878) n (%)	Denosumab 120 mg Q4W (N=878) n (%)	Zoledronic Acid 4 mg Q4W (N=945) n (%)	Denosumab 120 mg Q4W (N=943) n (%)	Zoledronic Acid 4 mg Q4W (N=2836) n (%)	Denosumab 120 mg Q4W (N=2841) n (%)
Pain	97 (9.6)	72 (7.1)	52 (5.9)	57 (6.5)	94 (9.9)	93 (9.9)	243 (8.6)	222 (7.8)
Urinary tract infection	92 (9.1)	72 (7.1)	46 (5.2)	43 (4.9)	124 (13.1)	105 (11.1)	262 (9.2)	220 (7.7)
Thrombocytopenia	60 (5.9)	68 (6.7)	102 (11.6)	96 (10.9)	37 (3.9)	52 (5.5)	199 (7.0)	216 (7.6)
Anxiety	74 (7.3)	75 (7.4)	58 (6.6)	75 (8.5)	52 (5.5)	46 (4.9)	184 (6.5)	196 (6.9)
Rash	100 (9.9)	97 (9.5)	76 (8.7)	67 (7.6)	25 (2.6)	29 (3.1)	201 (7.1)	193 (6.8)
Musculoskeletal chest pain	81 (8.0)	82 (8.0)	52 (5.9)	54 (6.2)	55 (5.8)	50 (5.3)	188 (6.6)	186 (6.5)
Depression	86 (8.5)	72 (7.1)	56 (6.4)	62 (7.1)	40 (4.2)	52 (5.5)	182 (6.4)	186 (6.5)
Dehydration	42 (4.1)	46 (4.5)	70 (8.0)	68 (7.7)	52 (5.5)	65 (6.9)	164 (5.8)	179 (6.3)
Paraesthesia	73 (7.2)	69 (6.8)	60 (6.8)	46 (5.2)	71 (7.5)	53 (5.6)	204 (7.2)	168 (5.9)
Abdominal pain upper	82 (8.1)	71 (7.0)	39 (4.4)	51 (5.8)	43 (4.6)	45 (4.8)	164 (5.8)	167 (5.9)
Leukopenia	76 (7.5)	81 (7.9)	73 (8.3)	51 (5.8)	28 (3.0)	33 (3.5)	177 (6.2)	165 (5.8)
Rib fracture	93 (9.2)	83 (8.1)	46 (5.2)	40 (4.6)	27 (2.9)	35 (3.7)	166 (5.9)	158 (5.6)
Pleural effusion	62 (6.1)	64 (6.3)	49 (5.6)	52 (5.9)	26 (2.8)	37 (3.9)	137 (4.8)	153 (5.4)
Myalgia	106 (10.5)	82 (8.0)	32 (3.6)	31 (3.5)	57 (6.0)	37 (3.9)	195 (6.9)	150 (5.3)
Nasopharyngitis	94 (9.3)	84 (8.2)	31 (3.5)	25 (2.8)	38 (4.0)	40 (4.2)	163 (5.7)	149 (5.2)

Table 27.continued

Preferred Term	Study 20050136		Study 20050244		Study 20050103		Overall	
	Zoledronic Acid 4 mg Q4W (N=1013) n (%)	Denosumab 120 mg Q4W (N=1020) n (%)	Zoledronic Acid 4 mg Q4W (N=878) n (%)	Denosumab 120 mg Q4W (N=878) n (%)	Zoledronic Acid 4 mg Q4W (N=945) n (%)	Denosumab 120 mg Q4W (N=943) n (%)	Zoledronic Acid 4 mg Q4W (N=2836) n (%)	Denosumab 120 mg Q4W (N=2841) n (%)
Thoracic vertebral fracture	78 (7.7)	64 (6.3)	46 (5.2)	38 (4.3)	30 (3.2)	47 (5.0)	154 (5.4)	149 (5.2)
Hypertension	65 (6.4)	67 (6.6)	43 (4.9)	33 (3.8)	45 (4.8)	48 (5.1)	153 (5.4)	148 (5.2)
Neuropathy peripheral	71 (7.0)	71 (7.0)	42 (4.8)	46 (5.2)	29 (3.1)	30 (3.2)	142 (5.0)	147 (5.2)
Pneumonia	43 (4.2)	32 (3.1)	56 (6.4)	67 (7.6)	31 (3.3)	48 (5.1)	130 (4.6)	147 (5.2)
Stomatitis	71 (7.0)	90 (8.8)	32 (3.6)	33 (3.8)	12 (1.3)	23 (2.4)	115 (4.1)	146 (5.1)
Dyspepsia	74 (7.3)	52 (5.1)	39 (4.4)	38 (4.3)	34 (3.6)	42 (4.5)	147 (5.2)	132 (4.6)
Hypokalaemia	51 (5.0)	40 (3.9)	65 (7.4)	55 (6.3)	40 (4.2)	35 (3.7)	156 (5.5)	130 (4.6)
Neck pain	71 (7.0)	66 (6.5)	38 (4.3)	29 (3.3)	35 (3.7)	30 (3.2)	144 (5.1)	125 (4.4)

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N = Number of subjects who received ≥ 1 active dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
Preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA Version 12.1.
[a] Includes all adverse events, not only those occurring with ≥ 5% frequency

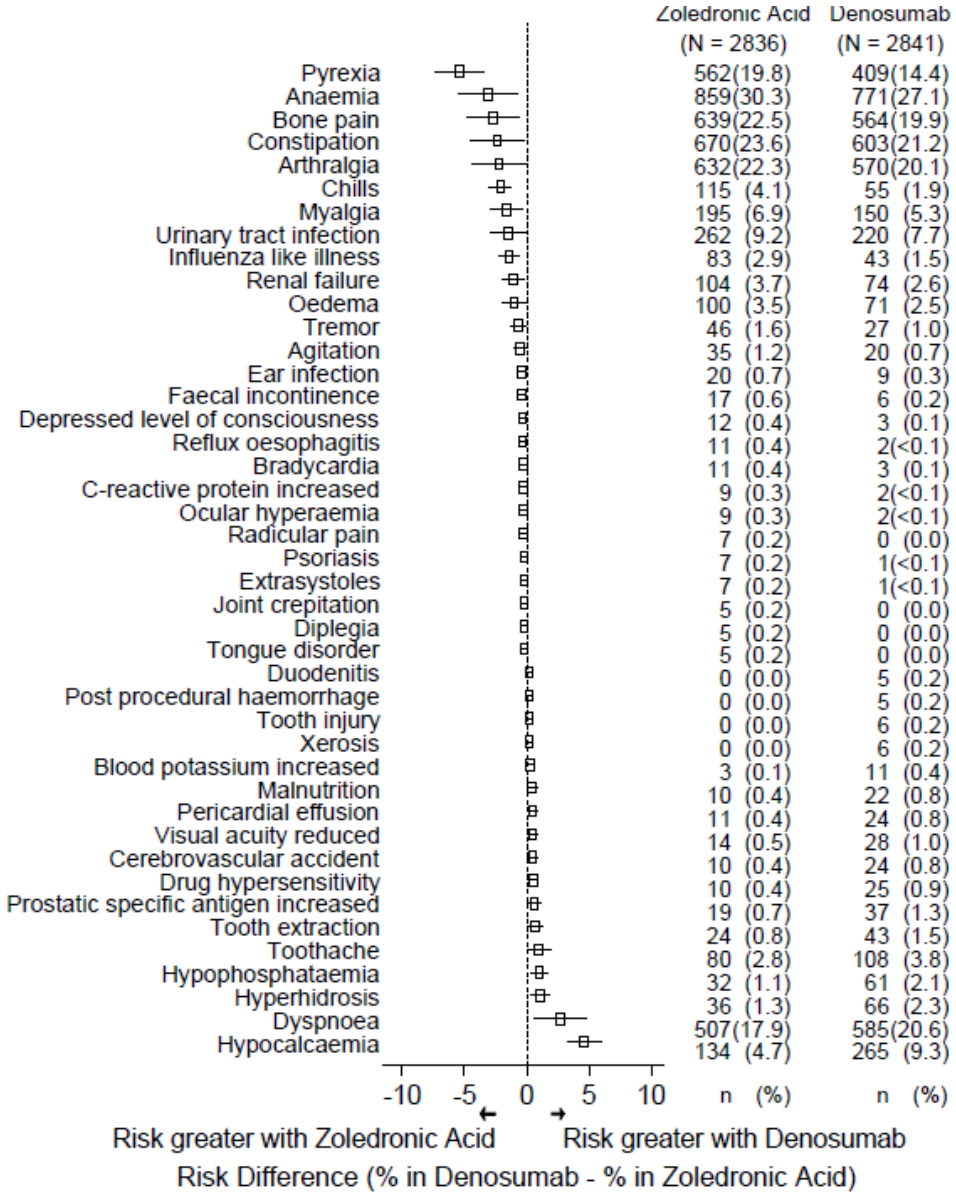
A Forest plot demonstrating comparisons of AE incidences by p value and risk difference (not adjusted for multiplicity) is shown in Figure 28 below.

The incidence of AEs judged to be treatment related was 29.1% in the denosumab group and 33.1% in the zoledronic acid group. The most common treatment related AEs in each treatment group were hypocalcaemia (5.7% for denosumab versus 2.7% for zoledronic acid), fatigue (2.7% for denosumab compared with 3.5% for zoledronic acid), nausea (2.6% for denosumab versus 4.6% for zoledronic acid) and pyrexia (1.2% for denosumab compared with 7.1% for zoledronic acid).

Dyspnoea showed an unexpectedly higher incidence in the denosumab group (20.6% versus 17.9%). Given the non specific nature of this PT, further analysis of this symptom was conducted. Exertional dyspnoea was reported equally between the two treatment groups (2.0% for denosumab versus 1.9% for zoledronic acid). Serious AEs of dyspnoea were reported in 5.1% of subjects in the denosumab group versus 4.2% for the zoledronic acid patient group. The trial with the highest incidence of reported dyspnoea was Study 2005-0244 (denosumab 25.5% versus zoledronic acid 22.8%) and this trial involved a significant proportion of subjects with lung cancer (39.5% in the denosumab arm and 39.6% of subjects in the zoledronic acid group) which may have been a confounding factor. Lung metastasis at baseline was more common in the denosumab arm in this study (27.0% versus 18.2%) which may be an explanation for the difference seen for this AE. Analysis of the SAEs of dyspnoea revealed acute precipitating events in 96% of subjects, which were generally variable and multifactorial in nature (for example, pleural effusion, disease progression, pneumonia, congestive heart failure and severe anaemia). The sponsor's assessment that the increase in dyspnoea reported is not likely to be of clinical significance would seem plausible.

Likewise, hyperhidrosis was reported more frequently in the denosumab treatment group (2.3% versus 1.3%). Almost all cases were of mild to moderate severity. The clinical significance of this AE in uncertain but it is unlikely to be clinically relevant.

Figure 28. Forest Plot of Adverse Events with P value <0.05 (unadjusted for multiplicity) by Preferred Term (primary advanced cancer safety analysis set)



N = Number of subjects who received >= 1 active dose of investigational product; n = Number of subjects reporting >= 1 event. Unadjusted p-value is calculated from Cochran-Armitage test stratified by study.
Risk difference is based on Mantel-Haenszel method adjusting for the stratification variable of study.

Adverse events pre identified by the sponsor as being of special interest are discussed in detail below.

Supportive Phase II-III Studies

In addition to the three pivotal Phase III trials, five studies contributed supportive safety data to this submission.

Phase II Dose-Ranging Studies 2004-0113 and 2004-0114

Study 2004-0113 enrolled 255 female subjects (212 were given various doses of denosumab (as per the PK review) and 43 received IV bisphosphonate) with breast cancer and no prior bisphosphonate exposure. Patients were given up to 25 weeks of study drug treatment followed by a 32 week post treatment follow-up period (57 weeks on study in

total). Most (95%) subjects in any treatment group reported at least one AE during the study. Adverse events occurring with at least a 10% difference in incidence between the combined denosumab groups and IV bisphosphonate arm included asthenia (16% for denosumab versus 28% with bisphosphonate), arthralgia (11% for denosumab versus 30% with bisphosphonate), pyrexia (9% for denosumab versus 21% with bisphosphonate) and myalgia (4% for denosumab versus 21% with bisphosphonate). A total of 32 subjects (15%) in the denosumab groups and 8 patients (19%) in the bisphosphonate group died, mostly due to underlying malignancy. Similar proportions of subjects in each pooled treatment group recorded SAEs (39-40%) and no discernible treatment related pattern of events was evident. The overall incidence of hypocalcaemia and the different grades of severity were evenly matched between the two treatment groups although there was only one subject who received denosumab 180 mg every 4 weeks who developed severe hypocalcaemia.

Study 2004-0114 treated 108 patients with either denosumab 180 mg every 12 weeks (n=35), denosumab 180 mg every 4 weeks (n=38) or IV bisphosphonate (n=35) for up to 25 weeks initially and possibly 105 weeks in the extension phase. Subjects had various types of solid tumours (excluding lung) or MM and had received IV bisphosphonate for at least 8 weeks immediately prior to inclusion in this trial. Again, most (97%) of subjects in any treatment group reported at least one AE during the study. Common AEs reported at similar frequencies for each of the three treatment groups included bone pain (34-37%), anaemia (20-26%), nausea (20-24%), constipation (17-26%) and asthenia (18-23%). No dose related trend for AEs was observed for denosumab. Four subjects given denosumab (1 [35] for 12 week dosing and 3 [8%] for 4 week dosing) and 3 (9%) given bisphosphonate withdrew from the study because of AEs. Serious AEs were observed in 37 patients (overall 51%) given denosumab (46% for 12 week dosing and 55% for 4 week dosing) and 19 subjects (54%) administered IV bisphosphonate. Hypocalcaemia was recorded as an AE for 7 (10%) denosumab treated patients and 2 (6%) subjects receiving bisphosphonate. One hypocalcaemic event was serious (in a patient receiving denosumab every 4 weeks). There were no cases of osteonecrosis of the jaw (ONJ). Infections (29-37%) and serious infections (6-7%) occurred in similar proportions of patients in each of the three treatment groups.

Open-label Phase II Studies

Study 2005-0134 involved 96 denosumab treated patients with relapsed (n=53) or plateau phase (n=43) multiple myeloma who were actively treated until disease progression (expected to be at least 6 x 28 cycles of therapy or 168 days) or withdrawal. Most (89%) patients reported at least one AE with the most common type of side effects being upper respiratory tract infection (21%), anaemia (19%) and fatigue (17%). In total, five subjects withdrew from treatment because of AEs and one of these events was significant because the patient (treated for plateau phase MM) developed pneumonia and subsequently died. In addition, one subject treated for relapsed MM developed ONJ. Two patients with plateau phase MM also experienced significant hypocalcaemia.

Study 2004-0215 recruited 37 adult subjects with histologically confirmed giant cell tumour of the bone who all received denosumab 120 mg SC every 4 weeks (with loading doses on Days 1, 8 and 15) until either complete tumour resection, disease progression or discontinuation. Again, most (89%) of patients reported at least one AE with the common events being extremity pain (19%), back pain (11%), headache (11%), diarrhoea (5%) and hypocalcaemia (5%). Five (14%) subjects experienced SAEs which included two cases of severe dyspnoea. One patient died during the trial because of disease progression (lung metastasis).

Interim Safety Report for Study 2005-0147

This is a blinded Phase III study which involves 1435 men with histologically confirmed, hormone refractory prostate cancer who have been chemically or surgically castrated and have a total serum testosterone of less than 50 mg/dL (1.72 nmol/L). The subjects are at high risk of developing bone metastasis and the objective of the study is to determine whether denosumab can prolong bone metastasis free survival. As of the data cut off date (30 October 2009), 61% (873/1435) of patients had discontinued from denosumab. Thus far, the incidence of SAEs is 43% (619/1435) with the most commonly reported events being Renal/Urinary disorders (226 patients, 16%), Neoplasms (128 subjects, 9%), Infections (109 patients, 8%), Cardiac disorders (95 subjects, 7%), Gastrointestinal disorders (88 patients, 6%) and Administration site conditions (71 subjects, 5%). Most of the urinary disorders were episodes of urinary retention (85 patients, 6%). As of the data cut off date, 147 patients (10%) had died and the sub typing of fatal events indicates that most of deaths were disease rather than drug related.

Serious adverse events (SAE) and deaths

A serious adverse event was considered as any AE that resulted in death, was life-threatening, required prolonged hospitalisation, resulted in significant disability or incapacity or was a congenital anomaly or birth defect. Other events considered medically significant by the study investigators were also included as an SAE.

The overall incidence of SAE was similar between the two treatment groups (56.3% for denosumab versus 57.1% for zoledronic acid). Reflective of the underlying prognosis of enrolled subjects, the incidence of SAE was higher in Study 2005-0103 (63% for denosumab versus 60.1% for zoledronic acid) and Study 2005-0244 (63% for denosumab versus 60.1% for zoledronic acid) than in Study 2005-0136 (44.4% for denosumab versus 46.5% for zoledronic acid).

The incidences of SAE by Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term (PT) are listed in Table 28. Events with increased incidence in the denosumab group include ‘dyspnoea’ (144/2841 subjects [5.1%] versus 120/2836 subjects [4.2%]), ‘pneumonia’ (112 subjects [3.9%] versus 93 subjects [3.3%]), ‘respiratory failure’ (89 subjects [3.1%] versus 74 subjects [2.6%]) and ‘osteonecrosis’ (39 subjects [1.4%] versus 19 subjects [0.7%]).

Table 28. Common Reported Serious Adverse Events in Phase III Advanced Cancer Studies. Reported for ≥1% of subjects in either treatment group by Preferred Term in descending order of frequency. Primary Advanced Cancer Safety Analysis set.

	Study 20050136		Study 20050244		Study 20050103		Overall	
Preferred Term	Zoledronic Acid 4 mg Q4W (N=1013) n (%)	Denosumab 120 mg Q4W (N=1020) n (%)	Zoledronic Acid 4 mg Q4W (N=878) n (%)	Denosumab 120 mg Q4W (N=878) n (%)	Zoledronic Acid 4 mg Q4W (N=945) n (%)	Denosumab 120 mg Q4W (N=943) n (%)	Zoledronic Acid 4 mg Q4W (N=2836) n (%)	Denosumab 120 mg Q4W (N=2841) n (%)
Number of subjects reporting serious adverse events	471 (46.5)	453 (44.4)	581 (66.2)	552 (62.9)	568 (60.1)	594 (63.0)	1620 (57.1)	1599 (56.3)
Anaemia	32 (3.2)	27 (2.6)	49 (5.6)	25 (2.8)	82 (8.7)	108 (11.5)	163 (5.7)	160 (5.6)
Dyspnoea	38 (3.8)	53 (5.2)	54 (6.2)	55 (6.3)	28 (3.0)	36 (3.8)	120 (4.2)	144 (5.1)
Pneumonia	25 (2.5)	20 (2.0)	44 (5.0)	52 (5.9)	24 (2.5)	40 (4.2)	93 (3.3)	112 (3.9)
Malignant neoplasm progression	7 (0.7)	6 (0.6)	100 (11.4)	103 (11.7)	3 (0.3)	2 (0.2)	110 (3.9)	111 (3.9)
Metastases to central nervous system	46 (4.5)	47 (4.6)	44 (5.0)	43 (4.9)	6 (0.6)	14 (1.5)	96 (3.4)	104 (3.7)
Respiratory failure	20 (2.0)	20 (2.0)	40 (4.6)	45 (5.1)	14 (1.5)	24 (2.5)	74 (2.6)	89 (3.1)
Dehydration	24 (2.4)	13 (1.3)	34 (3.9)	35 (4.0)	19 (2.0)	36 (3.8)	77 (2.7)	84 (3.0)
Vomiting	31 (3.1)	31 (3.0)	24 (2.7)	21 (2.4)	22 (2.3)	24 (2.5)	77 (2.7)	76 (2.7)
General physical health deterioration	15 (1.5)	20 (2.0)	38 (4.3)	26 (3.0)	28 (3.0)	29 (3.1)	81 (2.9)	75 (2.6)
Asthenia	14 (1.4)	12 (1.2)	16 (1.8)	21 (2.4)	29 (3.1)	37 (3.9)	59 (2.1)	70 (2.5)
Pyrexia	26 (2.6)	21 (2.1)	21 (2.4)	26 (3.0)	18 (1.9)	19 (2.0)	65 (2.3)	66 (2.3)
Pleural effusion	25 (2.5)	24 (2.4)	27 (3.1)	23 (2.6)	9 (1.0)	12 (1.3)	61 (2.2)	59 (2.1)
Spinal cord compression	8 (0.8)	6 (0.6)	26 (3.0)	27 (3.1)	33 (3.5)	24 (2.5)	67 (2.4)	57 (2.0)
Back pain	14 (1.4)	8 (0.8)	19 (2.2)	15 (1.7)	36 (3.8)	29 (3.1)	69 (2.4)	52 (1.8)
Pulmonary embolism	18 (1.8)	11 (1.1)	18 (2.1)	19 (2.2)	16 (1.7)	20 (2.1)	52 (1.8)	50 (1.8)
Metastases to liver	28 (2.8)	20 (2.0)	13 (1.5)	16 (1.8)	5 (0.5)	13 (1.4)	46 (1.6)	49 (1.7)
Febrile neutropenia	22 (2.2)	17 (1.7)	31 (3.5)	21 (2.4)	8 (0.8)	8 (0.8)	61 (2.2)	46 (1.6)
Fatigue	5 (0.5)	15 (1.5)	6 (0.7)	11 (1.3)	10 (1.1)	20 (2.1)	21 (0.7)	46 (1.6)
Bone pain	13 (1.3)	10 (1.0)	15 (1.7)	11 (1.3)	34 (3.6)	24 (2.5)	62 (2.2)	45 (1.6)
Diarrhoea	16 (1.6)	19 (1.9)	13 (1.5)	14 (1.6)	13 (1.4)	12 (1.3)	42 (1.5)	45 (1.6)
Urinary tract infection	9 (0.9)	7 (0.7)	9 (1.0)	9 (1.0)	30 (3.2)	28 (3.0)	48 (1.7)	44 (1.5)
Nausea	23 (2.3)	21 (2.1)	16 (1.8)	14 (1.6)	14 (1.5)	8 (0.8)	53 (1.9)	43 (1.5)
Abdominal pain	14 (1.4)	15 (1.5)	17 (1.9)	18 (2.1)	12 (1.3)	8 (0.8)	43 (1.5)	41 (1.4)
Hypocalcaemia	2 (0.2)	5 (0.5)	8 (0.9)	12 (1.4)	7 (0.7)	24 (2.5)	17 (0.6)	41 (1.4)
Neutropenia	14 (1.4)	16 (1.6)	11 (1.3)	14 (1.6)	4 (0.4)	10 (1.1)	29 (1.0)	40 (1.4)
Thrombocytopenia	11 (1.1)	12 (1.2)	23 (2.6)	17 (1.9)	5 (0.5)	10 (1.1)	39 (1.4)	39 (1.4)
Osteonecrosis	11 (1.1)	18 (1.8)	4 (0.5)	7 (0.8)	4 (0.4)	14 (1.5)	19 (0.7)	39 (1.4)
Renal failure	9 (0.9)	1 (<0.1)	13 (1.5)	10 (1.1)	28 (3.0)	26 (2.8)	50 (1.8)	37 (1.3)
Cardiac failure	7 (0.7)	6 (0.6)	5 (0.6)	10 (1.1)	23 (2.4)	21 (2.2)	35 (1.2)	37 (1.3)
Multi-organ failure	9 (0.9)	9 (0.9)	8 (0.9)	10 (1.1)	18 (1.9)	18 (1.9)	35 (1.2)	37 (1.3)
Urinary retention	0 (0.0)	1 (<0.1)	9 (1.0)	3 (0.3)	35 (3.7)	32 (3.4)	44 (1.6)	36 (1.3)
Hepatic failure	16 (1.6)	24 (2.4)	4 (0.5)	2 (0.2)	6 (0.6)	10 (1.1)	26 (0.9)	36 (1.3)
Prostate cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	56 (5.9)	34 (3.6)	56 (2.0)	34 (1.2)
Pain	8 (0.8)	4 (0.4)	6 (0.7)	12 (1.4)	12 (1.3)	16 (1.7)	26 (0.9)	32 (1.1)
Haematuria	0 (0.0)	0 (0.0)	2 (0.2)	8 (0.9)	37 (3.9)	23 (2.4)	39 (1.4)	31 (1.1)
Decreased appetite	8 (0.8)	10 (1.0)	7 (0.8)	7 (0.8)	13 (1.4)	13 (1.4)	28 (1.0)	30 (1.1)
Sepsis	4 (0.4)	2 (0.2)	11 (1.3)	16 (1.8)	11 (1.2)	12 (1.3)	26 (0.9)	30 (1.1)
Renal failure acute	6 (0.6)	0 (0.0)	15 (1.7)	10 (1.1)	16 (1.7)	18 (1.9)	37 (1.3)	28 (1.0)
Chest pain	9 (0.9)	5 (0.5)	10 (1.1)	14 (1.6)	13 (1.4)	9 (1.0)	32 (1.1)	28 (1.0)
Deep vein thrombosis	8 (0.8)	4 (0.4)	13 (1.5)	15 (1.7)	8 (0.8)	8 (0.8)	29 (1.0)	27 (1.0)
Cachexia	7 (0.7)	6 (0.6)	10 (1.1)	4 (0.5)	12 (1.3)	14 (1.5)	29 (1.0)	24 (0.8)
Pain in extremity	3 (0.3)	8 (0.8)	7 (0.8)	5 (0.6)	20 (2.1)	10 (1.1)	30 (1.1)	23 (0.8)
Disease progression	12 (1.2)	11 (1.1)	13 (1.5)	8 (0.9)	2 (0.2)	0 (0.0)	27 (1.0)	19 (0.7)

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N = Number of subjects who received ≥ 1 active dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
Preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA Version 12.1.

Adverse events (including SAE) of special interest

A series of AEs were identified by the sponsor as being of special interest and are discussed individually below.

Hypocalcaemia

Bone metabolism plays an important role in maintaining homeostasis of serum calcium. Therefore, hypocalcaemia is of importance as an AE with denosumab treatment given its mechanism in suppressing bone metabolism. Hypocalcaemia is an established AE of zoledronic acid, although most cases are generally asymptomatic and transient. Similarly, previous Phase I, II and III trials of denosumab for postmenopausal osteoporosis demonstrated a transient 3-8% decline in serum calcium within the first two weeks of drug treatment.

Significant hypocalcaemia is more likely to occur when oral absorption of calcium is impaired, such as when dietary intake is insufficient or due to vitamin D deficiency (which regulates absorption of oral calcium). Effective vitamin D deficiency may also occur in moderate to severe renal impairment due to deficient conversion of the inactive form of vitamin D (cholecalciferol) to the activated form (calcitriol). It is important to note that in all of the clinical trials submitted for evaluation, oral calcium and vitamin D supplementation was strongly encouraged (unless the subject was hypercalcaemic). Additionally, subjects with significant renal impairment (CrCl < 30 mL/min) were excluded from the trials. Compliance with these measures in a non trial setting may not match that of a clinical trial, potentially underestimating the prevalence of this AE in routine treatment.

Also of note is the following advice given to study centres for the three pivotal Phase III studies, "In general, abnormal laboratory findings without clinical significance (based on the study investigator's judgment) should not be recorded as adverse events; however, laboratory value changes requiring therapy or adjustment in prior therapy are considered adverse events."

This advice is likely to have reduced the overall incidence of hypocalcaemia, however, the reporting is likely to better reflect the clinically relevant events. Routine serum calcium monitoring is reported in the laboratory measurements section below.

Four PTs ('hypocalcaemia', 'blood calcium decreased', 'calcium deficiency' and 'ionized calcium decreased') which are essentially equivalent in their meaning were used in recording of the safety data and are combined under the term 'hypocalcaemia' for this evaluation.

Hypocalcaemia was more common with denosumab treatment than zoledronic acid therapy using the Primary Safety Analysis Set, for both the integrated dataset (273 subjects [9.6%] versus 141 subjects [5.0%]), and the individual studies (Study 2005-0103 [12.8% versus 5.8%]; Study 2005-0136 [5.6% versus 3.5%]; Study 2005-0244 [10.8% versus 5.8%]). The incidence of hypocalcaemia was lower in the breast cancer study (2005-0136) than in the other two pivotal studies. Most hypocalcaemia events occurred during the first six months of treatment (187 subjects compared to 91 subjects).

While the majority of events were classified as being of mild to moderate severity (>60% in both treatment arms), 41 subjects (1.4%) in the denosumab arm and 18 subjects (0.6%) in the zoledronic acid arm experienced severe hypocalcaemia.

Most cases of hypocalcaemia resolved with no specific treatment or oral calcium alone, however 104 subjects (3.6%) in the denosumab arm and 47 (1.7%) in the zoledronic acid group received treatment with IV calcium.

While most cases of hypocalcaemia were mild and of little clinical significance, the two fold increase in incidence of both serious adverse events and the need for IV replacement of calcium in the denosumab group would suggest that the rate of clinically relevant hypocalcaemia is significantly higher with the proposed denosumab treatment regimen compared with the currently utilised zoledronic acid regimen. This is significant, both from a patient safety point of view as well as an ease of administration perspective, as the need for heightened monitoring of serum calcium and increased IV calcium infusions negates some of the benefits of the subcutaneous administration route of denosumab over IV zoledronic acid.

Osteonecrosis of the Jaw

ONJ is a potentially serious adverse event that has been reported in subjects treated with bisphosphonates with apparent risk factors for its development including cumulative dose of treatment, advanced cancer and tooth extraction. The pathophysiology is not clearly defined, however suppression of bone turnover has been hypothesised as being important.

All events reported as ONJ, or a pre specified series of corresponding AE PTs, were selected for adjudication by an independent committee. In addition, information entered on oral examination case report forms was also used for selection of cases for adjudication. All cases adjudicated as being positive were reported to regulatory authorities in an expedient manner.

In the Primary Advanced Cancer Safety Analysis set, the overall incidence of positively adjudicated ONJ was 52 subjects (1.8%) in the denosumab group and 37 subjects (1.3%) in the zoledronic acid group. Although a trend to increased incidence is seen, on statistical analysis, incidence was not found to be significantly different, both overall (p=0.1343) and for the individual studies (Study 2005-0103 p=0.0864; Study 2005-0136 p=0.3876; Study 2005-0244 p=1.0).

The overall incidence of all reported events of the PT 'osteonecrosis' was 52 subjects (1.8%, 41 adjudicated positive) in the denosumab arm and 34 subjects (1.2%, 27 adjudicated positive) in the zoledronic acid group. All of these cases were in the jaw, apart from three cases involving the hip (each confounded by bone metastasis of the hip).

Surgical procedures such as curettage were required for approximately half the subjects in each group with positive adjudicated ONJ. Three subjects in the denosumab group and one in the zoledronic acid group required bone resection. Of the positively adjudicated cases, 33 subjects in the denosumab group and 22 subjects in the zoledronic acid group discontinued treatment due to ONJ.

Most (81% in both groups) subjects with positively adjudicated ONJ had a history of tooth extraction, poor oral hygiene and/or use of a dental appliance. Other potential associations in the denosumab and zoledronic groups respectively included prior or current use of antiangiogenic medications (6 (11.5%) and 8 (21.6%) subjects); prior or current chemotherapy (36 (69.2%) and 27 (73%) subjects); and prior or current use of bisphosphonates (1 (1.9%) and 4 (10.8%) subjects).

Osteonecrosis of the jaw is a serious adverse event and although rare, the safety data presented would support that the risk of ONJ with denosumab is at least as great as that for zoledronic acid. A trend towards increased incidence, although not statistically significant, suggests that the risk with the proposed denosumab regimen may even be greater.

Infection

RANKL is expressed on activated T and B cells in human lymph nodes. Infection is therefore a theoretical risk with denosumab. The exact role of RANKL in the immune response is not clear, however it would appear from non-clinical models that its role is not essential.[26,27,28,29] No evidence of immunosuppression or increased risk of infections was apparent in primate studies of denosumab. An increase in AEs and SAE for infection was seen in the post menopausal studies compared with placebo (257 subjects receiving denosumab versus 226 subjects receiving control for overall infectious AE; and for infectious SAEs 43 subjects receiving denosumab and 33 subjects given control therapy, respectively). Given the association of RANKL with the immune system, infection was pre specified as an AE of special interest.

In the Primary Advanced Cancer Safety Analysis Set, the overall incidence of AEs related to infections was similar between the treatment arms (43.4% for denosumab versus 42.9% for zoledronic acid). The most common infections reported were urinary tract infections (7.7% for denosumab and 9.2% zoledronic acid), nasopharyngitis (5.2% for denosumab and 5.7% with zoledronic acid) and pneumonia (5.2% for denosumab compared with 4.6% for zoledronic acid). A small increase in infections reported in the denosumab group compared to zoledronic acid was seen in Studies 2005-0244 (40.8% versus 39.7%) and 2005-0103 (42.6% versus 39.7%) with a small comparative decrease seen in Study 2005-0136 (46.4% versus 48.8%).

A small trend to an increased incidence of serious infection related AEs was observed in the denosumab arm (329/2841 subjects [11.6%] for denosumab versus 309/2836 subjects [10.9%] for zoledronic acid). The most common infectious SAEs by PT were pneumonia (3.9% for denosumab compared with 3.3% for zoledronic acid), urinary tract infections (1.5% with denosumab versus 1.7% for zoledronic acid) and sepsis (1.1% for denosumab versus 0.9% for zoledronic acid). As per Overall infections, the incidence of serious infections was relatively higher for denosumab in Studies 2005-0244 (14.6% versus 13.4%) and 2005-0103 (13.8% versus 11.4%) and comparatively lower for denosumab in Study 2005-0136 (7.0% versus 8.2%). Of additional note is the lower incidence of serious infection in Study 2005-0136 (for both therapies), which reflects the overall better prognosis of subjects enrolled in this trial.

Considering the common serious infections further, the incidence of pneumonia in the individual studies reflected the incidence of infections overall, being higher in Studies 2005-0244 (5.9% with denosumab versus 5.0% for zoledronic acid) and 2005-0103 (4.2% for denosumab versus 2.5% with zoledronic acid) and comparatively lower in Study 2005-0136 (2.0% for denosumab versus 2.5% with zoledronic acid). The sponsor reports that almost all these events occurred in subjects with risk factors for pneumonia (advanced age; history of cardiovascular disease or diabetes; and concomitant medications such as

[26] Loser K, Mehling A, Loeser S. *et al.* Epidermal RANKL controls regulatory T cell numbers via activation of dendritic cells. *Nat Med* 2006; 12: 1372-9.

[27] Padigel UM, Kim N, Choi Y, Farrell JP. TRANCE-RANK costimulation is required for IL-12 production and the initiation of a Th1-type response to Leishmania major infection in CD40-deficient mice. *J Immunol* 2003; 171: 5437-5441.

[28] Green EA, Choy Y, Flagella RA. Pancreatic lymph node-derived CD4(+)CD25(+) Treg cells: highly potent regulators of diabetes that require TRANCE-RANK signals. *Immunity* 2002; 16: 183-91.

[29] Bachmann MF, Wong BR, Josien R. *et al*. TRANCE, a tumour necrosis family member critical for CD40 ligand-independent T helper cell activation. *J Exp Med* 1999; 189: 1025-1031.

corticosteroids, chemotherapy and/or opioids). This observation may explain the lower incidence of pneumonia in Study 2005-0136, whereby prognosis was generally better than the other two trials. Fatality related to pneumonia was similar if both treatment groups (0.5%). Serious pneumonia resulting in study withdrawal was low, 0.1% for subjects in either treatment group. When all the PTs relating to Lower respiratory tract infections are grouped together, a small trend to increased incidence remains for denosumab (147/2841 subjects [5.2%]) compared to zoledronic acid (116/2836 subjects [4.1%]).

Due to an increased incidence of Serious skin infections (but not Overall infections) in a Phase III trial of denosumab for post menopausal osteoporosis (Study 2003-0216), a specific analysis of Skin infections was performed in this program. Studies with mouse keratinocytes suggest that blocking RANKL in mice decrease the number of regulatory T-cells in skin, leading to an increased inflammatory response.[20] It is possible that the increased risk of serious infections may represent an increased inflammatory response (leading to hospitalisation).

A marginal increase in the incidence of Skin infections was seen overall for denosumab compared with zoledronic acid (84/2841 subjects [3.0%] for denosumab versus 77/2836 subjects [2.7%] for zoledronic acid) from the Primary Advanced Cancer Safety Analysis Set; see Table 29). This was reflected in marginal increases in individual PTs of Skin infections: cellulitis (1.8% for denosumab versus 1.7% with zolendronic acid), erysipelas (0.6% with denosumab compared with 0.5% for zoledronic acid), skin infections (0.4% for both groups), subcutaneous abscesses (0.3% for denosumab versus 0.1% with zoledronic acid), infected skin ulcer (0.1% for denosumab versus <0.1% with zoledronic acid), impetigo (<0.1% versus 0%) and necrotising fasciitis (0% versus <0.1%).

Table 29. Incidence of all adverse events related to skin infection by Preferred Term

	Study 20050136		Study 20050244		Study 20050103		Overall	
Preferred Term	Zoledronic Acid 4 mg Q4W (N=1013) n (%)	Denosumab 120 mg Q4W (N=1020) n (%)	Zoledronic Acid 4 mg Q4W (N=878) n (%)	Denosumab 120 mg Q4W (N=878) n (%)	Zoledronic Acid 4 mg Q4W (N=945) n (%)	Denosumab 120 mg Q4W (N=943) n (%)	Zoledronic Acid 4 mg Q4W (N=2836) n (%)	Denosumab 120 mg Q4W (N=2841) n (%)
Number of subjects reporting adverse events of skin infection	35 (3.5)	33 (3.2)	15 (1.7)	20 (2.3)	27 (2.9)	31 (3.3)	77 (2.7)	84 (3.0)
Cellulitis	19 (1.9)	20 (2.0)	13 (1.5)	14 (1.6)	15 (1.6)	17 (1.8)	47 (1.7)	51 (1.8)
Erysipelas	8 (0.8)	10 (1.0)	0 (0.0)	2 (0.2)	6 (0.6)	5 (0.5)	14 (0.5)	17 (0.6)
Skin infection	5 (0.5)	5 (0.5)	1 (0.1)	2 (0.2)	4 (0.4)	4 (0.4)	10 (0.4)	11 (0.4)
Subcutaneous abscess	3 (0.3)	2 (0.2)	0 (0.0)	2 (0.2)	1 (0.1)	4 (0.4)	4 (0.1)	8 (0.3)
Infected skin ulcer	1 (<0.1)	1 (<0.1)	1 (0.1)	1 (0.1)	0 (0.0)	1 (0.1)	2 (<0.1)	3 (0.1)
Impetigo	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (<0.1)
Necrotising fasciitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	2 (<0.1)	0 (0.0)

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N = Number of subjects who received ≥ 1 active dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
Preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA Version 12.1.

Subject incidence of SAEs of Skin infections was modestly higher in the denosumab group (25/2841 subjects, 0.9%) than the zolendronic acid group (19/2836 subjects, 0.7%). For the individual PTs, cellulitis (18/2841 subjects [0.6%] versus 12/2836 subjects [0.4%]) and erysipelas (5 subjects [0.2%] versus 2 subjects [<0.1%]) displayed higher incidence in the denosumab group (Table 30). One fatality related to Skin infection occurred in each group.

Table 30. Serious adverse events related to skin infection

	Study 20050136		Study 20050244		Study 20050103		Overall	
Preferred Term	Zoledronic Acid 4 mg Q4W (N=1013) n (%)	Denosumab 120 mg Q4W (N=1020) n (%)	Zoledronic Acid 4 mg Q4W (N=878) n (%)	Denosumab 120 mg Q4W (N=878) n (%)	Zoledronic Acid 4 mg Q4W (N=945) n (%)	Denosumab 120 mg Q4W (N=943) n (%)	Zoledronic Acid 4 mg Q4W (N=2836) n (%)	Denosumab 120 mg Q4W (N=2841) n (%)
Number of subjects reporting adverse events of serious skin infection	5 (0.5)	9 (0.9)	5 (0.6)	7 (0.8)	9 (1.0)	9 (1.0)	19 (0.7)	25 (0.9)
Cellulitis	3 (0.3)	7 (0.7)	5 (0.6)	5 (0.6)	4 (0.4)	6 (0.6)	12 (0.4)	18 (0.6)
Erysipelas	1 (<0.1)	3 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.2)	2 (<0.1)	5 (0.2)
Skin infection	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	2 (0.2)	0 (0.0)	2 (<0.1)	2 (<0.1)
Subcutaneous abscess	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (<0.1)	1 (<0.1)
Infected skin ulcer	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Necrotising fasciitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	2 (<0.1)	0 (0.0)

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N = Number of subjects who received ≥ 1 active dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
Preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA Version 12.1.

A marginal increase in incidence of All systemic infections (sepsis, bacteraemia, viraemia and fungemia) in the denosumab group was also found (59/2841 [2.1%] subjects for denosumab versus 50/2836 [1.8%] subjects with zoledronic acid). Conversely, a marginal increase in Urinary tract infections in the zoledronic acid arm remains when all related PTs are considered (52/2841 subjects [1.8%] for denosumab versus 62/2836 subjects [2.2%] with zoledronic acid). No evidence of an increase in Opportunistic infections was seen in the sponsor's analysis.

While definitive evidence of an increased infection risk is not yet established, the trend to increased infections does appear to be a common feature of most of the denosumab trials. Evidence against a true AE risk is that the pattern of infections does not seem to be entirely consistent between trials. One interpretation of the variability in incidence of serious infection seen in the three pivotal cancer trials is that the increased incidence of serious infection in two studies may exist due to chance. However, an alternate explanation given the incidence is higher in the two studies that enrolled the poorest prognosis subjects is that denosumab may increase the risk of serious infection in those with pre existing underlying causes of immunosuppression. This explanation would be of concern given that subjects with very poor prognosis were excluded from participation in these trials. Postmarketing use would likely see a greater exposure in these very poor prognosis subjects. Overall, the potential increased risk of serious infection seems to be small; however the signal remains strong enough to continue to be of concern and will be monitored [30]

Malignancies

No carcinogenicity studies were performed in the denosumab clinical development program owing to a lack of recognition of denosumab for murine or rodent RANKL. There is no evidence of hyperplastic lesions in monkeys treated for up to 16 months. A slight increase in new malignancies was seen in the human trials for postmenopausal osteoporosis, namely those of gastrointestinal (n=35 with denosumab versus n=24 for placebo) and female reproductive (n=21 with denosumab versus n=9 for placebo; previous evaluation PM-2009-00390-3) malignancies. The sponsor contends that there is

[30] The sponsor considers this text to be speculative and it does not assist physician assessment of the product safety profile. The approved Xgeva Product Information document contains all relevant information concerning the incidence of skin infection.

no biologically plausible mechanism of carcinogenesis with denosumab and in fact the nonclinical studies suggest a possible anti mitotic effect.

New primary malignancies in the Primary Advanced Cancer Set were searched for in two ways:

- *Study 2005-0136* utilised a search strategy of malignancy PTs, excluding terms for benign malignancies, recurrent malignancies and disease progression
- *Studies 2005-0244* and *2005-0103* were determined by a blinded manual review of malignancy adverse events.

No integrated analysis was performed for new malignancies given the heterogeneity of the study populations. Disease progression and survival was considered as an exploratory efficacy endpoint and has been discussed in the *Efficacy* section.

The incidence of new malignancies in the in individual pivotal trials was:

- *Study 2005-0136*: 5 subjects (0.5%) in the denosumab arm versus 5 subjects (0.5%) treated with zoledronic acid,
- *Study 2005-0244*: 5 subjects (0.6%) receiving denosumab versus 3 subjects (0.3%) given zoledronic acid, and
- *Study 2005-0103*: 18 subjects (1.9%) receiving denosumab versus 10 subjects (1.1%) administered zoledronic acid.

Cumulatively, a total of 28 subjects (1.0%) developed new malignancy in the denosumab treatment groups versus 18 (0.6%) in the zoledronic acid arms. No pattern in terms of type of new malignancy was discerned, owing to one or two cases per treatment arm of each malignancy for each study. The sponsor considered one event (acute lymphocytic leukaemia) in a subject who received denosumab as potentially treatment related, with epirubicin suspected as a co contributor.

Hypersensitivity related adverse events

Being a monoclonal antibody, hypersensitivity is a theoretical possibility with denosumab. In the Phase III studies, 152 subjects (5.4%) in the denosumab arm and 108 subjects (3.8%) in the zoledronic acid group had AEs potentially associated with hypersensitivity reactions. Common PTs recording AEs related to hypersensitivity included face oedema (1.0% for denosumab and 0.6% with zoledronic acid), hypersensitivity (0.9% for denosumab and 0.7% with zoledronic acid), drug hypersensitivity (0.9% with denosumab versus 0.4% for zoledronic acid), urticaria (0.6% with denosumab and 0.5% for zoledronic acid) and face swelling (0.6% with denosumab and 0.4% for zoledronic acid). Most subjects experienced single events only. Of the reported AEs for 'drug hypersensitivity', only one subject in Study 2005-0103 was considered by the sponsor to have a causally related AE to denosumab. All other events were attributed to other medications known to cause drug hypersensitivity such as paclitaxel.

Serious adverse events related to hypersensitivity were reported in 14 subjects (0.5%) in the denosumab group and 8 (0.3%) in the zoledronic acid arm. Fatal events were reported in three subjects (0.1%) in the denosumab group (circulatory collapse) and two subjects in the zoledronic acid group (anaphylactic shock and circulatory collapse). None of these events were considered causally related to denosumab in the sponsor's analysis.

Overall, a small increase in incidence in hypersensitivity related adverse effects was seen for denosumab compared with zoledronic acid, however the risk of hypersensitivity reactions with denosumab appears to be low and generally of mild severity.

Eczema

An increased incidence of eczema was seen in Study 2003-0216 involving subjects with post menopausal osteoporosis. In the Phase III studies for cancer, the total incidence of eczema related PTs was 46/2836 subjects (1.6%) in the denosumab arm and 55/2841 subjects (1.9%) in the zoledronic acid treatment groups. Individual PTs were as follows: dermatitis (1.1% for denosumab versus 0.7% with zoledronic acid); dermatitis allergic (0.4% with denosumab versus 0.3% for zoledronic acid); eczema (0.3% with denosumab versus 0.5% for zoledronic acid), dermatitis contact (0.2% for denosumab versus 0.1% with zoledronic acid); and dermatitis atopic (0% versus <0.1%).

In the individual studies, combined PT incidences were 2.8% for denosumab compared with 2.9% for zoledronic acid for Study 2005-0136, 1.9% versus 0.8% in Study 2005-0244 and 1.0% versus 1.1% in Study 2005-0103.

High level group term incidences of epidermal and dermal conditions were similar between the two treatments (18.4% for denosumab versus 18.7% with zoledronic acid). A single subject in the zoledronic group had a serious event of eczema.

Overall, the safety analysis does not seem to suggest eczema as being an event of concern for denosumab.

Cataracts in Androgen Deprived Men with Prostate Cancer

Study 2004-0138, a three year placebo controlled trial of denosumab for the prevention of bone mineral density loss in prostate cancer subjects receiving androgen deprivation therapy found an increased incidence of cataracts (4.7% with denosumab versus 1.2% for placebo control). This finding was not replicated in Study 2005-0103 with a similar number of reported events in both groups (0.4% for denosumab versus 0.5% with zoledronic acid). A single serious event was reported in a subject who received zoledronic acid.

Acute Phase Reaction related adverse events

Acute phase reactions are a well established AE for zoledronic acid which may not be expected with denosumab. Acute phase reactions were searched by a predefined list of PTs occurring within three days of the initial dose of the investigational drug and for the first four weeks after drug initiation.

The subject incidence of events in the Primary Advanced Cancer Analysis Set was higher in the first three days after the first dose for zoledronic acid (20.2%) than for denosumab (8.7%). The effect was consistent across the three pivotal studies. The most common AE within the first three days of treatment was pyrexia (7.2% for zoledronic acid versus 0.6% with denosumab).

Serious adverse events potentially associated with acute phase reactions within the first three days of treatment were reported in <0.1% of denosumab treated subjects and 0.6% zoledronic acid treated subjects.

The subject incidence of adverse events related to acute phase reactions within the first 4 weeks of treatment was 35.7% in the zoledronic acid group and 26.0% in the denosumab group.

The results support a lower risk of acute phase reactions with denosumab than with zoledronic acid.

Cardiac/Vascular Disorders

Inconsistent results were observed in the nonclinical studies with respect to a possible link between RANKL inhibition and atherosclerotic plaque formation. Some human studies

however, suggest anti-RANKL medications may be protective in this regard. A link between zoledronic acid and atrial fibrillation has also been reported, although the balance of evidence is not supportive of this association.

In the advanced cancer Phase III studies, reported AE incidences in the Cardiac System Organ Class (SOC) were similar between the two treatment groups (381 subjects [13.4%] with denosumab and 380 subjects [13.4%] for zoledronic acid). The most common cardiac AEs were also balanced: tachycardia (2.8% with denosumab versus 2.6% for zoledronic acid), cardiac failure (1.7% for denosumab versus 1.8% with zoledronic acid), atrial fibrillation (1.5% with denosumab and 1.3% with zoledronic acid) and palpitations (1.1% for denosumab and 0.9% with zoledronic acid). A higher incidence of pericardial effusions was seen in the denosumab treatment groups (0.8% versus 0.4% with zoledronic acid). An analysis performed by the sponsor suggests that these events were 'largely attributable to underlying disease affecting the pericardium, metastases to the lung and pleura, or radiation to the mediastinum'.

Serious cardiac related adverse events were reported in 201 subjects (7.1%) in the denosumab arm and 192 (6.8%) in the zoledronic acid groups. The most common serious cardiac events were similarly matched between the two groups: cardiac failure (1.3% for denosumab and 1.2% with zoledronic acid), cardio respiratory arrest (0.6% for denosumab and 0.7% with zoledronic acid), congestive cardiac failure (0.5% in both groups) and cardiopulmonary failure (0.4% for denosumab versus 0.7% with zoledronic acid). Serious adverse events of pericardial effusions were found in 0.3% of patients receiving denosumab and 0.2% of subjects given zoledronic acid.

An increase in incidence of serious cardiac related adverse events in Study 2005-0244 was found (denosumab 8.8% compared with zoledronic acid 6.0%). The imbalance was not seen in the other two Phase III studies where the rate of serious cardiac related adverse events was slightly higher in the zoledronic acid group (Study 2005-0136: denosumab 3.3% versus zoledronic acid 4.0%; Study 2005-0103: 9.5% for denosumab versus 10.3% for zoledronic acid). The higher incidence of serious cardiac events in Study 2005-0244 was primarily driven by the PT 'cardiac arrest' (1.4% for denosumab compared with 0.3% with zoledronic acid). Blinded external adjudication of the cardiac arrest events in this study found 10 of the 12 events in the denosumab group and 2of the 3 events in the zolendronic acid group to be non cardiovascular in nature (event related to cancer progression, cancer related complications or unknown).

Fatal cardiac adverse events occurred in 99 subjects (3.5%) in the denosumab arm and 96 subjects (3.4%) in the zoledronic acid group with the individual PT Fatal AEs matched between treatment arms for the integrated dataset. Two subjects in the denosumab group (fatal cardiac failure) and one subject in the zoledronic acid arm (fatal acute myocardial infarction) had fatal cardiac events deemed to be potentially treatment related.

Vascular disorders were similar between treatment groups, including total incidence in the SOC (579 subjects [20.4%] for denosumab versus 596 subjects [21.0%] with zoledronic acid), SAEs (94 subjects [3.3%] with denosumab compared to 111 subjects [3.9%] for zoledronic acid) and Fatal events (8 subjects in both groups). No Fatal events were considered treatment related.

Individual PTs for vascular events were also similarly matched between treatment groups.

Renal Toxicity Related adverse events

Renal impairment in advanced cancer is common and generally multifactorial in etiology. Bisphosphonates such as zoledronic acid are associated with renal toxicity, particularly in those with pre existing renal impairment. It is important to note that subjects with CrCl <

30mL/min were excluded from the Phase III studies. Additionally, zoledronic acid doses were adjusted for renal impairment and subsequent doses were withheld if a pre specified rise in creatinine was seen in a subject. Denosumab therapy was not dose adjusted for renal impairment.

A higher incidence of renal toxicity was seen in the zoledronic acid group (335 subjects [11.8%] for zoledronic acid versus 262 subjects [9.2%] with denosumab). The most common renal AE by PT were 'blood creatinine increased' (3.7% for denosumab compared with 4.7% for zoledronic acid), 'renal failure' (2.6% with denosumab versus 3.7% for zoledronic acid), 'acute renal failure' (1.2% for denosumab versus 1.6% with zoledronic acid), 'renal impairment' (0.9% with denosumab versus 1.2% with zoledronic acid) and 'blood urea increased' (0.4% for denosumab versus 0.7% with zoledronic acid).

The overall incidence of renal SAEs was higher in the zoledronic acid group (2.9% for denosumab and 3.6% for zoledronic acid). Common serious adverse events by PT were 'renal failure' (1.3% for denosumab versus 1.8% with zoledronic acid), 'acute renal failure' (1.0% for denosumab versus 1.3% with zoledronic acid), 'blood serum creatinine increased' (0.3% for denosumab versus 0.1% with zoledronic acid), 'anuria' (0.1% for both groups), 'renal impairment' (<0.1% for denosumab versus 0.2% with zoledronic acid), 'azotemia' (<0.1% with denosumab versus 0.1% for zoledronic acid), 'chronic renal failure' (<0.1% for both groups) and 'oliguria' (<0.1% for both groups).

Fatal renal adverse events occurred in 15 subjects (0.5%) in the denosumab group and 16 subjects (0.6%) in the zoledronic acid group.

Subjects with baseline CrCl < 60mL/min had a higher incidence of renal adverse events in the zoledronic acid group (24.7% for zoledronic acid versus 7.9% with denosumab for all events; and 16.9% versus 6.3% for serious adverse events, respectively).

The sponsor believes the rate of renal adverse events in the denosumab treated patients reflects the underlying rate of renal events in an adult cancer population. While this opinion is plausible, placebo controlled trials are required to make a definitive statement of this nature. However, the safety data for the current Australian submission support a lower incidence of renal toxicity with denosumab compared with zoledronic acid.

Deaths

Fatality incidences related to AEs were similar overall between the two treatment groups (816/2841 subjects [28.7%] for denosumab versus 822/2836 subjects [29.0%] with zoledronic acid) and also in the individual studies (for *Study 2005-0103:* 30.0% for denosumab and 29.2% with zoledronic acid; *Study 2005-0136:* 20% with denosumab versus 21.2% with zoledronic acid; and *Study 2005-0244:* 37.5% for denosumab compared with 37.7% with zoledronic acid) for the Primary Advanced Cancer Safety Analysis Set. A high incidence of fatalities was seen in all three studies which is consistent with the enrolled subject population (metastatic cancer). Fatal adverse events were generally related to disease progression.

While an increase in incidence in fatal adverse events was seen for denosumab in some of the most frequently reported individual PTs, no specific pattern seems to be apparent to warrant suggestion of a treatment effect across the clinical trials (Table 31). This is particularly the case when the overall survival and disease progression data from the exploratory efficacy endpoints are considered, with no apparent difference seen between treatment groups (with the exception of the multiple myeloma subgroup). The differences seen in individual PTs are likely to be related to variations in the coding of the events rather than true AE incidences. Fatal AEs relevant to the pre specified adverse events of special interest are discussed in detail above.

The incidence of fatal AEs considered by the study investigators as potentially treatment related were slightly higher in the denosumab group (16 subjects [0.6%] versus 10 subjects [0.4%] for zoledronic acid). Individual PT events were generally isolated to single events in each trial (Table 32). Given the complexity of the medical history of subjects with advanced metastatic history and the confounding factor of variability of coding of reported events, it would be difficult to conclude an association for denosumab or zoledronic acid to any of these reported fatal adverse events.

Table 31. Fatal Adverse Events Reported in Phase III Advanced Cancer Studies

	Study 20050136		Study 20050244		Study 20050103		Overall	
Preferred Term	Zoledronic Acid 4 mg Q4W (N=1013) n (%)	Denosumab 120 mg Q4W (N=1020) n (%)	Zoledronic Acid 4 mg Q4W (N=878) n (%)	Denosumab 120 mg Q4W (N=878) n (%)	Zoledronic Acid 4 mg Q4W (N=945) n (%)	Denosumab 120 mg Q4W (N=943) n (%)	Zoledronic Acid 4 mg Q4W (N=2836) n (%)	Denosumab 120 mg Q4W (N=2841) n (%)
Number of subjects with fatal adverse events	215 (21.2)	204 (20.0)	331 (37.7)	329 (37.5)	276 (29.2)	283 (30.0)	822 (29.0)	816 (28.7)
Malignant neoplasm progression	6 (0.6)	4 (0.4)	75 (8.5)	87 (9.9)	3 (0.3)	2 (0.2)	84 (3.0)	93 (3.3)
Respiratory failure	16 (1.6)	19 (1.9)	29 (3.3)	29 (3.3)	10 (1.1)	18 (1.9)	55 (1.9)	66 (2.3)
Metastases to central nervous system	12 (1.2)	17 (1.7)	17 (1.9)	13 (1.5)	2 (0.2)	8 (0.8)	31 (1.1)	38 (1.3)
General physical health deterioration	8 (0.8)	11 (1.1)	23 (2.6)	13 (1.5)	13 (1.4)	11 (1.2)	44 (1.6)	35 (1.2)
Multi-organ failure	9 (0.9)	8 (0.8)	6 (0.7)	9 (1.0)	16 (1.7)	15 (1.6)	31 (1.1)	32 (1.1)
Hepatic failure	12 (1.2)	18 (1.8)	2 (0.2)	2 (0.2)	5 (0.5)	10 (1.1)	19 (0.7)	30 (1.1)
Metastases to liver	18 (1.8)	12 (1.2)	8 (0.9)	7 (0.8)	2 (0.2)	8 (0.8)	28 (1.0)	27 (1.0)
Cardiac failure	3 (0.3)	3 (0.3)	3 (0.3)	7 (0.8)	18 (1.9)	17 (1.8)	24 (0.8)	27 (1.0)
Dyspnoea	3 (0.3)	9 (0.9)	12 (1.4)	12 (1.4)	3 (0.3)	1 (0.1)	18 (0.6)	22 (0.8)
Prostate cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	43 (4.6)	21 (2.2)	43 (1.5)	21 (0.7)
Death	1 (<0.1)	2 (0.2)	8 (0.9)	6 (0.7)	10 (1.1)	11 (1.2)	19 (0.7)	19 (0.7)

	Study 20050136		Study 20050244		Study 20050103		Overall	
Preferred Term	Zoledronic Acid 4 mg Q4W (N=1013) n (%)	Denosumab 120 mg Q4W (N=1020) n (%)	Zoledronic Acid 4 mg Q4W (N=878) n (%)	Denosumab 120 mg Q4W (N=878) n (%)	Zoledronic Acid 4 mg Q4W (N=945) n (%)	Denosumab 120 mg Q4W (N=943) n (%)	Zoledronic Acid 4 mg Q4W (N=2836) n (%)	Denosumab 120 mg Q4W (N=2841) n (%)
Cachexia	6 (0.6)	3 (0.3)	6 (0.7)	1 (0.1)	9 (1.0)	11 (1.2)	21 (0.7)	15 (0.5)
Cardio-respiratory arrest	2 (0.2)	5 (0.5)	3 (0.3)	4 (0.5)	12 (1.3)	6 (0.6)	17 (0.6)	15 (0.5)
Pneumonia	2 (0.2)	0 (0.0)	7 (0.8)	11 (1.3)	5 (0.5)	4 (0.4)	14 (0.5)	15 (0.5)
Disease progression	8 (0.8)	8 (0.8)	12 (1.4)	6 (0.7)	1 (0.1)	0 (0.0)	21 (0.7)	14 (0.5)
Cardiac arrest	4 (0.4)	0 (0.0)	2 (0.2)	11 (1.3)	3 (0.3)	3 (0.3)	9 (0.3)	14 (0.5)
Metastases to bone	0 (0.0)	1 (<0.1)	1 (0.1)	3 (0.3)	6 (0.6)	9 (1.0)	7 (0.2)	13 (0.5)
Metastasis	3 (0.3)	9 (0.9)	3 (0.3)	1 (0.1)	1 (0.1)	2 (0.2)	7 (0.2)	12 (0.4)
Cardiopulmonary failure	4 (0.4)	2 (0.2)	8 (0.9)	7 (0.8)	6 (0.6)	2 (0.2)	18 (0.6)	11 (0.4)
Breast cancer	14 (1.4)	11 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	14 (0.5)	11 (0.4)
Pulmonary embolism	3 (0.3)	1 (<0.1)	3 (0.3)	3 (0.3)	2 (0.2)	6 (0.6)	8 (0.3)	10 (0.4)
Sepsis	2 (0.2)	1 (<0.1)	5 (0.6)	3 (0.3)	2 (0.2)	4 (0.4)	9 (0.3)	8 (0.3)
Cerebrovascular accident	2 (0.2)	1 (<0.1)	2 (0.2)	1 (0.1)	3 (0.3)	6 (0.6)	7 (0.2)	8 (0.3)
Prostate cancer metastatic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	13 (1.4)	7 (0.7)	13 (0.5)	7 (0.2)
Myocardial infarction	0 (0.0)	0 (0.0)	2 (0.2)	2 (0.2)	4 (0.4)	5 (0.5)	6 (0.2)	7 (0.2)
Performance status decreased	2 (0.2)	0 (0.0)	2 (0.2)	2 (0.2)	0 (0.0)	4 (0.4)	4 (0.1)	6 (0.2)

	Study 20050136		Study 20050244		Study 20050103		Overall	
Preferred Term	Zoledronic Acid 4 mg Q4W (N=1013) n (%)	Denosumab 120 mg Q4W (N=1020) n (%)	Zoledronic Acid 4 mg Q4W (N=878) n (%)	Denosumab 120 mg Q4W (N=878) n (%)	Zoledronic Acid 4 mg Q4W (N=945) n (%)	Denosumab 120 mg Q4W (N=943) n (%)	Zoledronic Acid 4 mg Q4W (N=2836) n (%)	Denosumab 120 mg Q4W (N=2841) n (%)
Renal failure acute	0 (0.0)	0 (0.0)	3 (0.3)	1 (0.1)	1 (0.1)	5 (0.5)	4 (0.1)	6 (0.2)
Renal failure	1 (<0.1)	0 (0.0)	2 (0.2)	4 (0.5)	6 (0.6)	1 (0.1)	9 (0.3)	5 (0.2)
Acute myocardial infarction	2 (0.2)	2 (0.2)	2 (0.2)	1 (0.1)	3 (0.3)	2 (0.2)	7 (0.2)	5 (0.2)
Septic shock	1 (<0.1)	0 (0.0)	3 (0.3)	4 (0.5)	3 (0.3)	1 (0.1)	7 (0.2)	5 (0.2)
Pleural effusion	1 (<0.1)	2 (0.2)	4 (0.5)	2 (0.2)	1 (0.1)	1 (0.1)	6 (0.2)	5 (0.2)
Hepatic function abnormal	5 (0.5)	5 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.2)	5 (0.2)
Respiratory distress	1 (<0.1)	2 (0.2)	2 (0.2)	2 (0.2)	0 (0.0)	1 (0.1)	3 (0.1)	5 (0.2)
Sudden death	0 (0.0)	1 (<0.1)	0 (0.0)	1 (0.1)	2 (0.2)	3 (0.3)	2 (<0.1)	5 (0.2)
Febrile neutropenia	0 (0.0)	2 (0.2)	0 (0.0)	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.2)
Breast cancer metastatic	10 (1.0)	4 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	10 (0.4)	4 (0.1)
Metastases to lung	5 (0.5)	1 (<0.1)	2 (0.2)	2 (0.2)	2 (0.2)	1 (0.1)	9 (0.3)	4 (0.1)
Asthenia	2 (0.2)	0 (0.0)	0 (0.0)	2 (0.2)	4 (0.4)	2 (0.2)	6 (0.2)	4 (0.1)
Pulmonary oedema	0 (0.0)	1 (<0.1)	2 (0.2)	2 (0.2)	3 (0.3)	1 (0.1)	5 (0.2)	4 (0.1)

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N = Number of subjects who received ≥ 1 active dose of investigational product
n = Number of subjects with ≥ 1 event
Includes only treatment-emergent adverse events
Preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA Version 12.1.
All deaths due to disease progression may not be included.

Table 32. Fatal Adverse Events Considered Potentially Treatment Related In Phase III Advanced Cancer Studies.

	Study 20050136		Study 20050244		Study 20050103		Overall	
Preferred Term	Zoledronic Acid 4 mg Q4W (N=1013) n (%)	Denosumab 120 mg Q4W (N=1020) n (%)	Zoledronic Acid 4 mg Q4W (N=878) n (%)	Denosumab 120 mg Q4W (N=878) n (%)	Zoledronic Acid 4 mg Q4W (N=945) n (%)	Denosumab 120 mg Q4W (N=943) n (%)	Zoledronic Acid 4 mg Q4W (N=2836) n (%)	Denosumab 120 mg Q4W (N=2841) n (%)
Number of subjects with investigational product-related fatal adverse events	4 (0.4)	5 (0.5)	3 (0.3)	6 (0.7)	3 (0.3)	5 (0.5)	10 (0.4)	16 (0.6)
Respiratory failure	0 (0.0)	1 (<0.1)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	3 (0.1)
Death	0 (0.0)	0 (0.0)	2 (0.2)	1 (0.1)	0 (0.0)	1 (0.1)	2 (<0.1)	2 (<0.1)
Cachexia	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (<0.1)	1 (<0.1)
Cardiac failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	1 (<0.1)	1 (<0.1)
Pulmonary embolism	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (<0.1)	1 (<0.1)
Acute hepatic failure	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Acute respiratory distress syndrome	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Disseminated intravascular coagulation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (<0.1)
Hepatic failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Hepatic function abnormal	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Ischaemic stroke	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Metastases to central nervous system	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)

	Study 20050136		Study 20050244		Study 20050103		Overall	
Preferred Term	Zoledronic Acid 4 mg Q4W (N=1013) n (%)	Denosumab 120 mg Q4W (N=1020) n (%)	Zoledronic Acid 4 mg Q4W (N=878) n (%)	Denosumab 120 mg Q4W (N=878) n (%)	Zoledronic Acid 4 mg Q4W (N=945) n (%)	Denosumab 120 mg Q4W (N=943) n (%)	Zoledronic Acid 4 mg Q4W (N=2836) n (%)	Denosumab 120 mg Q4W (N=2841) n (%)
Renal failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Acute myocardial infarction	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Acute respiratory failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (<0.1)	0 (0.0)
Haemolytic anaemia	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Prostate cancer metastatic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (<0.1)	0 (0.0)
Pulmonary haemorrhage	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)

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N = Number of subjects who received ≥ 1 active dose of investigational product
n = Number of subjects with ≥ 1 event
Includes only treatment-emergent adverse events for which the investigator indicated there was a reasonable possibility they may have been caused by investigational product
Preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA Version 12.1.

Overall Survival Analyses

Overall survival analysis from the exploratory efficacy endpoints is relevant to the discussion of safety for the current Australian submission. Statistical power was sufficient in the integrated analysis to provide 98% power to detect a 15% increase in risk and 84% power to detect a 10% increase in risk. Survival data was not available from those subjects who fully withdrew consent or who were lost to follow up, with similar dropout rates between treatment groups (see Table 33). Overall (HR 0.99; 95% CI 0.91-1.07; p=0.712) and across the three individual pivotal Phase III trials, no significant difference of treatment on mortality was seen (see Kaplan-Meier curves, Figure 29).

Figure 29. Overall Survival Kaplan-Meier Curves For Phase III Advanced Cancer Studies. N= number of subjects randomised.

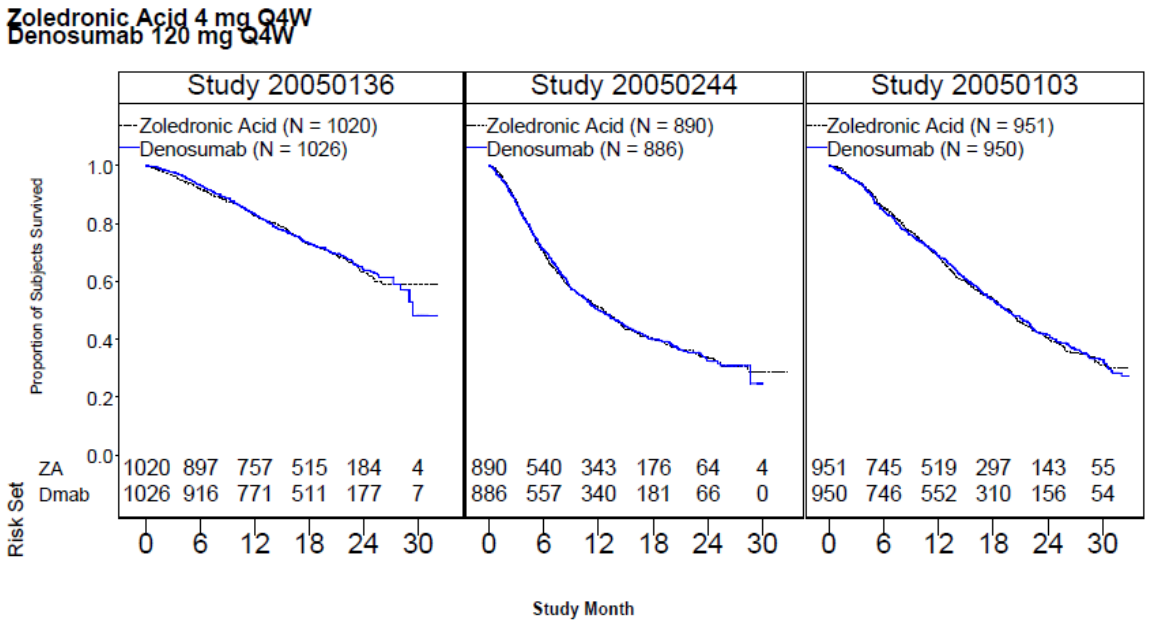

Table 33. Subjects Not Available for Survival Analysis (due to withdrawn consent or lost to follow-up) in the Phase III Advanced Cancer Studies

Study ID	Denosumab		Zolendronic Acid	
	Subjects	Percentage	Subjects	Percentage
2005-0103	156	16.4%	177	18.6%
2005-0136	126	12.3%	124	12.2%
2005-0244	146	16.5%	159	17.9%

Overall Survival in the Multiple Myeloma Subtype

Of relevance is a post hoc analysis of tumour subtype in Study 2005-0244. This has been discussed previously in the *Efficacy* section but it is relevant to the safety analysis that there was a significantly increased risk of death in the multiple myeloma subgroup (HR 2.26; 95% CI 1.13-4.5). Analysis of factors accounting for this difference provided by the sponsor suggest that differences in baseline disease characteristics (including impaired renal function), stem cell transplant therapy and withdrawals and loss to follow up may 'partially explain the difference observed between treatment groups'.

Examining the baseline demographics of the MM subgroup provided it was noted that more geriatric subjects are found in the zoledronic acid group (≥65 years: 47.3% for zoledronic acid versus 39.5% with denosumab; ≥75 years: 16.1% for zoledronic acid versus 7% with denosumab). While less baseline Stage I disease and ECOG status 0 is found in the denosumab group (8.2% for denosumab versus 14% with zoledronic acid; and 23.3% versus 32.3%, respectively), there was a modest increase prevalence of Stage II disease and ECOG Status 2 in the zoledronic acid group (60.2% for zoledronic acid compared with 57.6% with denosumab; and 19.4% versus 17.4%, respectively). The mean time from diagnosis to first bone metastasis was also less in the zoledronic acid group (3.8 months versus 5.9 months), suggesting a potentially more aggressive disease manifestation. The mean time from diagnosis to randomisation was also greater in the

zoledronic acid group (7.2 months versus 5.6 months). From these baseline disease characteristics it would be difficult to suggest an imbalance that would favour zoledronic acid. Baseline renal function (Table 34) does not seem to support a difference favouring zoledronic acid either. Significantly greater rates of stem cell transplant did however occur in the zoledronic acid arm (24.7% versus 16.3%).

Table 34. Baseline Renal Function in the Multiple Myeloma Subgroup

	Zoledronic Acid 4 mg Q4W (N = 93)	Denosumab 120 mg Q4W (N = 86)	All (N = 179)
Calculated creatinine clearance level - n (%)			
< 15 mL/min	0 (0.0)	0 (0.0)	0 (0.0)
15 - < 30 mL/min	0 (0.0)	0 (0.0)	0 (0.0)
30 - < 60 mL/min	23 (24.7)	10 (11.6)	33 (18.4)
60 - < 90 mL/min	35 (37.6)	33 (38.4)	68 (38.0)
≥ 90 mL/min	31 (33.3)	43 (50.0)	74 (41.3)
Missing	4 (4.3)	0 (0.0)	4 (2.2)

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N = Number of subjects randomized
[a] Albumin-adjusted calcium will only be adjusted if albumin level is less than 4 g/dL
Cockcroft-Gault formula was applied to estimate creatinine clearance.

The sponsor is correct in asserting that these subgroup analyses are inconclusive given their ad hoc nature and lack of a specific randomisation control for survival factors and anti neoplastic treatments. However, the data does raise a genuine concern, particularly given the different disease biology of MM compared with solid cancer metastasis. The data provided is not sufficient at this stage to support safety in subjects with MM. It is noted that the sponsor intends to conduct a specific Phase III study in subjects with MM.

Laboratory findings

Laboratory evaluations were graded using the National Cancer Institute Common Terminology Criteria (version 3.0)[31] with subject incidences reported being the worst criteria grade reported during the subject's enrolment.

Albumin adjusted serum calcium

As discussed in the section on hypocalcaemia, both denosumab and zoledronic acid would be expected to cause transient decrease in serum calcium. Median calcium values were within normal ranges throughout the study. Median serum calcium decreases were approximately ≤ 5% at each time point through the study.

The incidence of low serum calcium values were higher for subjects in the denosumab group compared with zoledronic acid as seen in Table 35. The results are consistent with the increased risk of hypocalcaemia reported in the clinical AEs section.

[31] Common Terminology Criteria (CTC) is a standardised classification of side effects used in assessing drugs for cancer therapy, in particular. Specific conditions and symptoms may have values or descriptive comment for each level, but the general guideline is 1 – Mild, 2 – Moderate, 3 – Severe, 4 - Life threatening, 5 - Death.

Table 35. Subject Incidence of CTCAE Grade II-IV Hypocalcaemia in the Phase III Advanced Cancer Studies

Laboratory Parameters	Relationship to Normal	Grade	Zoledronic Acid 4 mg Q4W (N = 2836) n (%)	Denosumab 120 mg Q4W (N = 2841) n (%)
Calcium (Corrected)	Below	Grade 2	111 (3.9)	265 (9.3)
		Grade 3	33 (1.2)	72 (2.5)
		Grade 4	5 (0.2)	16 (0.6)

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N = Number of subjects who received ≥ 1 active dose of investigational product
The maximum toxicity grade experienced by each subject based on the Common Terminology Criteria for Adverse Events, version 3.0

Serum Creatinine

Subjects with baseline CrCl < 30 mL/min were excluded from the pivotal studies. Median creatinine values were similar between the two treatment groups and remained so throughout the various trials. Median creatinine values were also within normal range at baseline and throughout the study. The incidence of Grade I-IV elevated serum creatinine was greater in the zoledronic acid group (20.9%) than the denosumab group (17.0%), consistent with the known AE profile of zoledronic acid.

Safety in special populations

Pregnancy and Lactation

No studies have been conducted in pregnant or lactating women as this was a common exclusion criterion for all trials. However, a total of four healthy women became pregnant during the early phase bioequivalence studies. All of the subjects received a single 60 mg dose of denosumab and were identified as being pregnant 2-3 months after drug administration. Two of the subjects gave birth to healthy infants and the outcome of the other two pregnancies is unknown. As part of its pharmacovigilance plan (outline in the Risk Management Plan-version 1.0), the sponsor proposes a surveillance program for women who become pregnant within 12 months of drug administration

Paediatric Population

No studies have been conducted in subjects aged less than 18 years. Study 2006-2004 is an unreported, ongoing trial recruiting skeletally mature adolescents (aged 12-17 years) with giant cell tumours of bone. The sponsor also plans to commence a study in patients aged 0-17 years with bone metastases to assess the efficacy of denosumab in the prevention of SRE in addition to collecting safety data (as per EMA request).

Geriatric Subjects

Denosumab has already been provisionally evaluated in patients aged > 65 years and > 75 years as part of the clinical trial program for the current Australian application. In total, 2583 subjects (1323 given zoledronic acid 4 mg every 4 weeks and 1280 received at least 1 dose of denosumab 120 mg every 4 weeks) who participated in the cancer studies were aged more than 65 years and 951 of these subjects were at least 75 years of age. No differences were observed between treatment groups or across age subgroups (< 65 years versus >65 years) in the overall incidence of AEs or SAEs.

Effect of Race

Of the 2841 patients who received denosumab in the integrated safety dataset for malignancy, 2404 subjects (84.6%) were Caucasian (2633.7 patient years (PY) of exposure), 153 (5.4%) were Hispanic (154.3 PY), 83 (2.9%) were Black or African American (86.1 PY), 89 (3.1%) were non-Japanese Asian (75.5 PY), 72 (2.5%) were Japanese (101.4 PY) and the remainder were of other ethnic backgrounds (such as Pacific Islander). No consistent difference between treatment groups was observed for the type or incidence of AEs or SAEs in the racial subgroups. Patients with either a Hispanic or Black ethnic background appeared to have a slightly higher incidence of overall AE compared to other race subgroups but the overall numbers were too small to draw meaningful conclusions.

Subjects with Renal Impairment

Denosumab is not expected to have an effect on renal function as RANKL has no known role or expression in the kidney. Patients with a baseline creatinine clearance of less than 30 mL/min were excluded from the trials and those with a GFR of less than 60 mL/min received dose adjusted zoledronic acid. Changes with renal function while receiving study treatment have been discussed previously in the Clinical section of this AusPAR. However, as renal function declines, the potential for the development of hypocalcaemia increases with either investigated treatment. The reason for the association between advancing moderate to severe renal impairment and an increased risk of hypocalcaemia is unclear but putatively relates to changes in vitamin D utilization.

Immunological events

The incidence of immunogenicity to denosumab is low and does not appear to be associated with any clinical sequelae (particularly, safety events) or demonstrable changes in pharmacology. Sensitive and specific assays for detecting anti drug antibodies were developed and validated for the nonclinical and clinical study programs. In general, blood samples were initially screened for binding antibodies using an immunoassay method and if positive, were then checked for neutralizing antibodies using a cell based messenger ribonucleic acid (mRNA) expression assay. In the nonclinical studies, high rates of binding (35-76%) and neutralizing (20-47%) anti-drug antibodies were identified in primates treated with denosumab for six or more months. The main effect of the anti drug antibodies in these animals was increased drug clearance and subsequent loss of PD effect. However, in the clinical studies involving adult human subjects, the incidence of immunogenicity was very low with only 0.3% (10 of 3508) of patients developing binding anti drug antibodies after receiving at least one dose of denosumab. Five of these subjects were transiently positive and tested negative at their last tested time point. The other five patients were positive at only the last time point tested. Neutralizing antibodies were not detected in any subject.

Safety related to drug-drug interactions and other interactions

No specific drug interaction studies have been conducted with denosumab. Given that the compound is a monoclonal antibody which is not eliminated via hepatic metabolism, no direct drug-drug interactions are anticipated. Furthermore, the three pivotal studies were conducted in patients receiving background standard of care for their disease(s) which involved a range of chemotherapy drugs, analgesics and other medicines. The likelihood of drug interactions between denosumab and other concurrently administered monoclonal antibodies such as trastuzumab and bevacizumab is low given the specificities of such treatments and the body's large capacity for IgG catabolism.

However, as RANKL is a cytokine and some other cytokines (such as interleukin-1 (IL-1) and IL-6) have been shown to regulate cytochrome P450 (CYP), a potential role for RANKL in altering CYP expression is possible because of secondary effects on inflammatory cytokines. Upon request from the FDA, the sponsor plans to conduct a drug drug interaction study with midazolam (a CYP3A4 substrate probe) in women with post menopausal osteoporosis to investigate the potential risk.

Discontinuation due to Adverse Events

Adverse events led to a discontinuation of investigational drug treatment in 12.4% of denosumab treated subjects and 13.1% of subjects receiving zoledronic acid in the Phase III adult cancer studies. Withdrawal from the study due to AEs occurred in 9.5% of subjects treated with denosumab and 9.9% of subjects given zoledronic acid. The most common AEs (by PT) resulting in withdrawal are summarised in Table 36.

The two most common reasons for discontinuation, osteonecrosis and hypocalcaemia, were more common in the denosumab group compared with zoledronic acid group (31 subjects [1.1%] versus 18 subjects [0.6%]; and 20 subjects [0.7%] versus 1 subject [<0.1%], respectively). These two AEs have otherwise been discussed in the section on AEs of special interest.

Table 36. Most Common Adverse Events Leading to Investigational Product Withdrawal in Phase III Advanced Cancer Studies

	Study 20050136		Study 20050244		Study 20050103		Overall	
Preferred Term	Zoledronic Acid 4 mg Q4W (N=1013) n (%)	Denosumab 120 mg Q4W (N=1020) n (%)	Zoledronic Acid 4 mg Q4W (N=878) n (%)	Denosumab 120 mg Q4W (N=878) n (%)	Zoledronic Acid 4 mg Q4W (N=945) n (%)	Denosumab 120 mg Q4W (N=943) n (%)	Zoledronic Acid 4 mg Q4W (N=2836) n (%)	Denosumab 120 mg Q4W (N=2841) n (%)
Number of subjects reporting adverse events leading to investigational product discontinuation	125 (12.3)	98 (9.6)	109 (12.4)	91 (10.4)	138 (14.6)	164 (17.4)	372 (13.1)	353 (12.4)
Osteonecrosis	7 (0.7)	12 (1.2)	7 (0.8)	5 (0.6)	4 (0.4)	14 (1.5)	18 (0.6)	31 (1.1)
Hypocalcaemia	1 (<0.1)	4 (0.4)	0 (0.0)	4 (0.5)	0 (0.0)	12 (1.3)	1 (<0.1)	20 (0.7)
General physical health deterioration	5 (0.5)	4 (0.4)	9 (1.0)	5 (0.6)	9 (1.0)	10 (1.1)	23 (0.8)	19 (0.7)
Fatigue	6 (0.6)	6 (0.6)	1 (0.1)	6 (0.7)	6 (0.6)	5 (0.5)	13 (0.5)	17 (0.6)
Asthenia	3 (0.3)	2 (0.2)	9 (1.0)	3 (0.3)	8 (0.8)	9 (1.0)	20 (0.7)	14 (0.5)
Malignant neoplasm progression	0 (0.0)	1 (<0.1)	13 (1.5)	12 (1.4)	0 (0.0)	0 (0.0)	13 (0.5)	13 (0.5)
Renal failure	4 (0.4)	0 (0.0)	4 (0.5)	1 (0.1)	4 (0.4)	11 (1.2)	12 (0.4)	12 (0.4)
Dyspnoea	5 (0.5)	5 (0.5)	5 (0.6)	6 (0.7)	1 (0.1)	1 (0.1)	11 (0.4)	12 (0.4)
Metastases to central nervous system	9 (0.9)	4 (0.4)	7 (0.8)	3 (0.3)	0 (0.0)	4 (0.4)	16 (0.6)	11 (0.4)
Anaemia	2 (0.2)	3 (0.3)	1 (0.1)	0 (0.0)	5 (0.5)	6 (0.6)	8 (0.3)	9 (0.3)

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N = Number of subjects who received ≥ 1 active dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events

Postmarketing experience

No postmarketing experience exists for denosumab for this indication.

Evaluator's overall conclusions on clinical safety

The data presented in the current Australian submission concerning the safety profile of denosumab treatment in adult patients with cancer (solid tumours and multiple myeloma) involving bone was of sufficient volume for assessment. In total, 2841 patients have received at least one dose of denosumab (at any dose) in the advanced cancer study program. Most of these subjects (n=2151) have received the commercially requested dose of 120 mg every 4 weeks for at least six months with 1535 patients being exposed for greater than 1 year.

Key safety conclusions identified by the clinical development program include:

- During the pivotal Phase III studies with up to 30 months of follow up, denosumab 120 mg SC given every 4 weeks in conjunction with background standard of care

treatment (chemotherapy and analgesics) was generally well tolerated with the overall incidence and most types of common recorded adverse events (apart from dyspnoea and hyperhydrosis) being similar in patients receiving infusions of zoledronic acid;

- Serious infections involving the lower respiratory tract and skin leading to hospitalization were more commonly recorded in subjects receiving denosumab (3.9% and 0.9%, respectively) in the controlled trials compared to those who received control treatment with zoledronic acid (3.3% and 0.7%, respectively);
- Overall serious adverse events occurred at a similar but high frequency in the denosumab and zoledronic acid treatment groups (56.3% compared to 57.1%, respectively);
- Osteonecrosis of the jaw was confirmed in 1.8% of patients given denosumab in the pivotal Phase III studies which is higher than that observed for subject receiving zoledronic acid (1.3%);
- Hypocalcaemia was reported for 9.6% of subjects treated with denosumab which was higher than that seen in patients who were administered zoledronic acid infusions (5.0%);
- Unexpectedly (and of unclear explanation), drug hypersensitivity reactions occurred with a slightly higher incidence in denosumab treated subjects (0.9% versus 0.4% for zoledronic acid);
- Discontinuations due to AEs were similar in the denosumab and zoledronic acid arms;
- Overall survival in patients with MM receiving denosumab appears to be reduced compared to those receiving zoledronic acid (HR 2.26) and this outcome appears to be multifactorial in explanation;
- The incidence and type of new malignancies is within cohort expectations and similar to that observed with zoledronic acid in the controlled studies;
- The development of persistently positive anti drug antibodies is very low (<0.3%) and is not associated with any clinical consequences.

In summary, the safety data indicates that denosumab treatment is generally well tolerated and has a comparable safety profile in short to medium term follow up compared to comparator treatment with intravenous zoledronic acid. However, some significant potential safety concerns are evident which will require ongoing pharmacovigilance. These risks include an increased risk of infection (including serious infection, mainly involving the respiratory tract and skin), osteonecrosis of the jaw, hypocalcaemia and drug hypersensitivity related reactions.

List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a List of Questions to the sponsor is generated.

Pharmacokinetics

1. Question: Could the sponsor please clarify why the PK data supports a fixed dose for denosumab versus a weight based dosing regimen?

Why has the sponsor came to conclusion that body weight was not a significant PK variable in dosing when the popPK studies suggest otherwise?

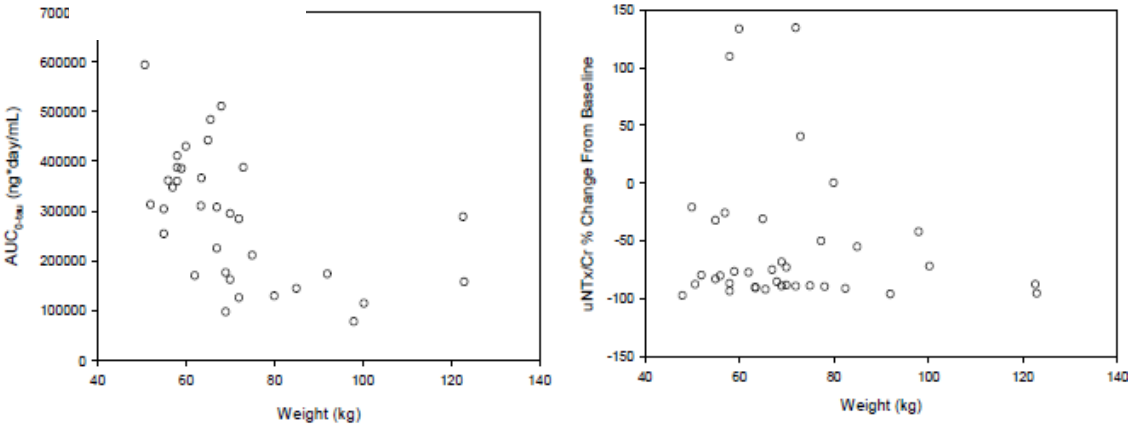
Sponsor response:

The denosumab pharmacokinetic data alone do not support the proposed fixed dose regimen. It is instead supported by the collective pharmacokinetic, pharmacodynamic

(bone resorption marker urine N-telopeptide corrected for urine creatinine [uNTx/Cr]), and efficacy data. Given the large inter-subject variability in pharmacokinetics for denosumab (also observed for other monoclonal antibodies), the observed trend of modestly lower exposure with body weight is not greater than the variability observed within subjects of a narrow weight range (for example, 60 to 70 kg, in Figure 30, left panel), with overlap across the weight range and comparable pharmacodynamic effects in the heavier subjects (Figure 30, right panel).

Figure 30.

Left panel: Denosumab $AUC_{0\text{-}tau}$ versus body weight (Study 20040113; 120 mg Q4W cohort; First dose. N=34). Right panel. Percent change in uNTX/Cr from baseline at Week 13 versus body weight (Study 20040113; 120 mg Q4W cohort; N=38).



$AUC_{0\text{-}tau}$ = Area under the serum concentration curve during the dosing interval
uNTx/Cr = urinary N-Telopeptide corrected for creatinine

As noted by the clinical evaluator, body weight was a covariate in the population pharmacokinetic analysis (for clearance and volume of distribution). Predictions based on the model indicate that denosumab steady state exposures for 120 mg fourth weekly dosing in 45 kg and 120 kg subjects are 48% higher and 46% lower, respectively, than exposures for a typical 66 kg subject. These approximately 50% differences should be considered in the context of the approximately 500% (5 fold) differences in exposure observed for subjects in a narrow weight range (for example, 60 to 70 kg in Figure 30). Thus, body weight was considered in dose selection for denosumab in the proposed indication, but as one of the many factors that contribute to large inter subject variability in exposures. Importantly, while body weight has a moderate effect on exposures that do not impact pharmacodynamic (uNTx/Cr) response, it also does not affect clinical response based on analyses from the pivotal Phase III SRE studies, as described below.

The three Phase III pivotal studies enrolled subjects with wide ranges of body weights within each treatment group (33 to 165 kg [median 73 kg] denosumab, 31 to 164 kg [median 73 kg] zoledronic acid). To assess the impact of weight on the efficacy of denosumab, the time to first on study SRE was analysed within baseline weight subgroups < 70 kg and ≥ 70 kg for the integrated efficacy dataset from the primary analysis of all three studies. This subgroup analysis demonstrated that the time to first on study SRE was generally longer for denosumab than zoledronic acid subjects regardless of weight (hazard ratios < 1) (Table 37), with no significant quantitative interaction detected. The hazard ratio was numerically lower and the relative risk reduction was higher for subjects with higher weight, which does not support a need for weight-based dosing. These results indicate that the direction of the treatment effect was consistent by weight and indicate that a fixed dose is appropriate from an efficacy perspective.

The primary endpoint of the time to first on study SRE was further analysed by baseline weight quartiles for the integrated efficacy dataset. The analysis by weight quartiles demonstrated that the time to first on study SRE was similar or longer for denosumab compared with zoledronic acid, regardless of weight (hazard ratios 0.75 to 1.01) (Table 38). There is no trend of changing hazard ratios with increasing weight quartiles. Amgen therefore considers that these results do not support a need for weight based dosing. As with the analysis by weight subgroups (< 70 kg and ≥ 70 kg), there was no significant quantitative interaction detected for the weight quartiles. These results by weight quartiles indicate that the magnitude and direction of the treatment effect was not impacted by weight and further indicate that a fixed dose is appropriate from an efficacy perspective.

In summary, these results lead to the conclusion that body weight is not a significant PK variable and support a fixed dose for denosumab versus a weight-based dosing regimen.

Table 37. Time to first SRE by baseline weight. Full Analysis set.

	Crude Incidence	KM Estimate of 25%-tile (Days)		KM Estimate of Median (Days)		Hazard Ratio[a]		
	n (%)	Pt Est	(95% CI)	Pt Est	(95% CI)	Pt Est	(95% CI)	p-value
Overall (unadjusted)								
Zoledronic Acid 4 mg Q4W (N = 2861)	1081 (37.8)	175.0	(169.00, 193.00)	592.0	(564.00, 652.00)			
Denosumab 120 mg Q4W (N = 2862)	934 (32.6)	230.0	(184.00, 254.00)	842.0	(737.00, NE)	0.83	(0.76, 0.90)	<.0001
Overall (adjusted for Weight Group)								
Zoledronic Acid 4 mg Q4W (N = 2861)	1081 (37.8)	175.0	(169.00, 193.00)	592.0	(564.00, 652.00)			
Denosumab 120 mg Q4W (N = 2862)	934 (32.6)	230.0	(184.00, 254.00)	842.0	(737.00, NE)	0.83	(0.76, 0.91)	<.0001
< 70 kg								
Zoledronic Acid 4 mg Q4W (N = 1152)	398 (34.5)	175.0	(169.00, 230.00)	679.0	(594.00, 799.00)			
Denosumab 120 mg Q4W (N = 1159)	364 (31.4)	176.0	(169.00, 253.00)	NE	(652.00, NE)	0.93	(0.80, 1.07)	0.3034

N = Number of subjects randomized; KM = Kaplan-Meier; NE = Not estimable
Hazard ratio < 1 favors denosumab.
[a] Based on a Cox proportional hazards model with treatment groups as the independent variable and stratified by study and the randomization stratification factors.
[b] Based on a Cox proportional model adding subgroup and subgroup-by-treatment interaction to [a].
p-value is for the superiority test of denosumab vs zoledronic acid.

	Crude Incidence	KM Estimate of 25%-tile (Days)		KM Estimate of Median (Days)		Hazard Ratio[a]		
	n (%)	Pt Est	(95% CI)	Pt Est	(95% CI)	Pt Est	(95% CI)	p-value
≥ 70 kg								
Zoledronic Acid 4 mg Q4W (N = 1691)	677 (40.0)	176.0	(168.00, 200.00)	564.0	(505.00, 597.00)			
Denosumab 120 mg Q4W (N = 1689)	568 (33.6)	246.0	(198.00, 270.00)	805.0	(680.00, NE)	0.78	(0.70, 0.88)	<.0001
Treatment-by-Weight Group interaction[b]								0.0826

N = Number of subjects randomized; KM = Kaplan-Meier; NE = Not estimable
Hazard ratio < 1 favors denosumab.
[a] Based on a Cox proportional hazards model with treatment groups as the independent variable and stratified by study and the randomization stratification factors.
[b] Based on a Cox proportional model adding subgroup and subgroup-by-treatment interaction to [a].
p-value is for the superiority test of denosumab vs zoledronic acid.

Table 38. Time to first SRE by baseline weight quartiles. Full Analysis set.

	Crude Incidence	KM Estimate of 25%-tile (Days)		KM Estimate of Median (Days)		Hazard Ratio[a]		
	n (%)	Pt Est	(95% CI)	Pt Est	(95% CI)	Pt Est	(95% CI)	p-value
Overall (unadjusted)								
Zoledronic Acid 4 mg Q4W (N = 2861)	1081 (37.8)	175.0	(169.00, 193.00)	592.0	(564.00, 652.00)			
Denosumab 120 mg Q4W (N = 2862)	934 (32.6)	230.0	(184.00, 254.00)	842.0	(737.00, NE)	0.83	(0.76, 0.90)	<.0001
Overall (adjusted for Weight Quartile)								
Zoledronic Acid 4 mg Q4W (N = 2861)	1081 (37.8)	175.0	(169.00, 193.00)	592.0	(564.00, 652.00)			
Denosumab 120 mg Q4W (N = 2862)	934 (32.6)	230.0	(184.00, 254.00)	842.0	(737.00, NE)	0.83	(0.76, 0.91)	<.0001
< 62.6 kg								
Zoledronic Acid 4 mg Q4W (N = 723)	250 (34.6)	174.0	(165.00, 224.00)	666.0	(577.00, 799.00)			
Denosumab 120 mg Q4W (N = 696)	201 (28.9)	201.0	(169.00, 262.00)	NE	(NE, NE)	0.87	(0.72, 1.05)	0.1583
62.6 kg - < 73.0 kg								
Zoledronic Acid 4 mg Q4W (N = 653)	228 (34.9)	179.0	(166.00, 254.00)	731.0	(574.00, NE)			
Denosumab 120 mg Q4W (N = 706)	246 (34.8)	190.0	(168.00, 258.00)	652.0	(554.00, NE)	1.01	(0.84, 1.22)	0.8906

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N = Number of subjects randomized; KM = Kaplan-Meier; NE = Not estimable
Hazard ratio < 1 favors denosumab.
[a] Based on a Cox proportional hazards model with treatment groups as the independent variable and stratified by study and the randomization stratification factors.
[b] Based on a Cox proportional model adding subgroup and subgroup-by-treatment interaction to [a].
p-value is for the superiority test of denosumab vs zoledronic acid.

	Crude Incidence	KM Estimate of 25%-tile (Days)		KM Estimate of Median (Days)		Hazard Ratio[a]		
	n (%)	Pt Est	(95% CI)	Pt Est	(95% CI)	Pt Est	(95% CI)	p-value
73.0 kg - < 84.0 kg								
Zoledronic Acid 4 mg Q4W (N = 734)	281 (38.3)	190.0	(172.00, 248.00)	562.0	(496.00, 685.00)			
Denosumab 120 mg Q4W (N = 692)	213 (30.8)	266.0	(183.00, 335.00)	NE	(681.00, NE)	0.75	(0.63, 0.90)	0.0023
≥ 84.0 kg								
Zoledronic Acid 4 mg Q4W (N = 733)	316 (43.1)	168.0	(121.00, 194.00)	532.0	(450.00, 595.00)			
Denosumab 120 mg Q4W (N = 754)	272 (36.1)	230.0	(176.00, 260.00)	805.0	(589.00, NE)	0.79	(0.67, 0.93)	0.0048
Treatment-by-Weight Quartile interaction[b]								0.1583

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N = Number of subjects randomized; KM = Kaplan-Meier; NE = Not estimable
Hazard ratio < 1 favors denosumab.
[a] Based on a Cox proportional hazards model with treatment groups as the independent variable and stratified by study and the randomization stratification factors.
[b] Based on a Cox proportional model adding subgroup and subgroup-by-treatment interaction to [a].
p-value is for the superiority test of denosumab vs zoledronic acid.

Efficacy

2. Question: Given the data for the multiple myeloma subgroup analysis, would the sponsor be prepared to withdraw this indication from its current application until further data becomes available to support such an indication? If so, then the proposed indication wording would need to be refined to specify solid tumours involving bone.

Sponsor response:

Amgen agrees to remove multiple myeloma from the indication for Xgeva.

The indication statement in the proposed Australian Product Information (PI) has, therefore, been amended in line with the United States PI as requested.

3. Comment: In the "Overall Conclusion on Efficacy" the clinical evaluator has commented that, "the efficacy results of the Phase III clinical trial program indicate a consistent response to denosumab treatment which is of modest clinical effect (prevention of further SRE but little change to overall survival or disease progression)." The effect of denosumab also is referred to as "modest" in several places throughout the Clinical Evaluation Report (CER).

Sponsor's Response:

Amgen disputes the evaluator's use of the term "modest" in reference to the clinical efficacy of denosumab and considers that all such future references should be replaced with "clinically meaningful superiority." Prevention of complications of bone metastases is distinct from effects on cancer outcomes, and bone targeted therapies, such as denosumab, are not expected to affect both similarly in patients with metastatic advanced cancer.

The objective of therapy with bone targeted agents in patients with advanced cancer is to reduce the skeletal complications that result from bone metastases. These complications include pathologic fracture, radiation to bone, surgery to bone, and spinal cord compression. Each of these events represents a clinically relevant complication of metastatic cancer in the skeleton caused by local bone destruction. Together, these events comprise the well accepted composite endpoint of skeletal related events, or SREs. This endpoint is accepted as clinically meaningful and represents the outcome that has resulted globally in registration of bisphosphonates in the prevention of SREs. Although the components of the SRE endpoint are complications that result from bone metastases, they do not necessarily represent disease progression in and of themselves. Overall disease progression and overall survival were therefore examined separately from the SRE endpoint in the denosumab studies, as they were in the three zoledronic acid studies that assessed disease outcomes.[32,33,34]

Efficacy results from the three Phase III pivotal studies (20050136, 20050244, and 20050103) showed a consistent and robust treatment effect of denosumab across tumour types for reduction in the occurrence of SREs. Specifically, the results for all SRE related endpoints, whether from the individual studies or the integrated analysis, demonstrated either superiority or directionally favourable efficacy for denosumab compared with the current standard of care, zoledronic acid. An 18% relative risk reduction in developing a first on study SRE was observed in Study 20050136, a 16% relative risk reduction was observed in Study 20050244, an 18% relative risk reduction was observed in Study 20050103 and a 17% relative risk reduction was observed in the integrated analysis. The effects of denosumab are clinically relevant, with a meaningful delay in experiencing a first on study SRE compared with zoledronic acid (not calculable in Study 20050136, 4.2 months in Study 20050244, 3.5 months in Study 20050103 and 8.2 months in the integrated analysis). The delays in experiencing a first SRE are particularly meaningful given the lifespan of patients with advanced cancer, which in these studies was a median of 22 months. Consistent with the improvement in time to first on study SRE, denosumab reduced the risk of developing first-and-subsequent on study SREs compared with zoledronic acid by 23%, 10%, 18%, and 18% for Studies 20050136, 20050244, and 20050103 and the integrated analysis, respectively. This endpoint is clinically highly relevant as the burden of complications from bone metastases extends well beyond the occurrence of the first SRE. Denosumab treatment resulted in a large reduction in the overall burden of SREs (426 events in approximately 5700 patients) and a risk reduction of 40% to 48% compared with placebo based on data from the zoledronic acid registration studies.

[32] Rosen LS, Gordon D, Tchekmedyian S. *et al*. (2003). Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: a phase III, double-blind, randomized trial - The Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group. *J Clin Oncol*. 21:3150-3157.
[33] Rosen LS, Gordon D, Kaminski M. *et al*. (2001). Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind, comparative trial. *Cancer*.7:377-387.
[34] Saad F, Gleason DM, Murray R. *et al*. (2002). A randomized placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst*. 94:1458-1468.

Overall survival and overall disease progression were balanced between denosumab and zoledronic acid in each study and in the integrated analyses. Anti resorptive agents are indicated for the prevention and delay of SREs and are not a priori cancer control agents: therefore, and as with zoledronic acid, it was not necessarily expected that denosumab would have a statistically significant improvement in terms of cancer outcomes in subjects with established bone metastases, despite significantly improving SRE outcomes.

In summary, prevention of SREs is clinically meaningful in patients with advanced cancer and bone metastases, and the superior efficacy of denosumab over zoledronic acid will have a clinical impact on patients. Prevention of complications of bone metastases is distinct from effects on cancer outcomes, and bone targeted therapies in patients with metastatic advanced cancer are not expected to affect both similarly. Therefore, Amgen disputes the evaluator's use of the term "modest" in reference to clinical efficacy and considers that all such future references should be replaced with "clinically meaningful superiority."

Safety

4. Question: What are the potential mechanistic explanations for an increased incidence of hypersensitivity reactions with denosumab versus zoledronic acid in the Phase III studies?

Sponsor response:

All monoclonal antibodies theoretically could be associated with hypersensitivity reactions. The risk is lower with fully human monoclonal antibodies like denosumab. Nonetheless, a conservative approach was undertaken to evaluate the potential for denosumab to result in hypersensitivity reactions in the clinical program.

A review of verbatim terms and timing of the adverse events potentially associated with hypersensitivity reported in the SRE studies showed that these events did not appear to be causally or temporally related to initiation of denosumab and, therefore, would not be considered mechanistically related to denosumab. Most subjects experienced single events, indicating that the events did not recur with continued treatment. All adverse events with the PT drug hypersensitivity were attributed to other medications (such as paclitaxel) that are known to be associated with drug hypersensitivity reactions with the exception of a single case in Study 20050103 (Subject 103191003). The subject was reported to have experienced an allergic reaction to investigational product beginning on Day 2, following the first and only dose of denosumab. The adverse events reported included urticaria, flushing, itching, rash, and bilateral ear lobe swelling. This event resolved following three days of treatment with oral antihistamines and methylprednisone. The subject was switched to zoledronic acid following this event and did not receive additional doses of denosumab. Although a relationship to denosumab is suggested in this particular case, it could not be confirmed since additional challenge with denosumab did not occur. Thus, Amgen considers that the higher incidence of hypersensitivity reactions in the Phase III studies was due to chance. A causal relationship to drug exposure has not been established.

Amgen will continue to monitor hypersensitivity reactions in clinical studies and in the postmarketing setting.

5. Clinical evaluator comment regarding Hypocalcaemia:

While most cases of hypocalcaemia were mild and of little clinical significance, the 2 fold increase in incidence of both serious adverse events and the need for IV replacement of calcium in the denosumab group would suggest that the rate of clinically relevant

hypocalcaemia is significantly higher with the proposed denosumab treatment regimen compared with the currently utilised zoledronic acid regimen. This is significant, both from a patient safety point of view as well as an ease of administration perspective, as the need for heightened monitoring of serum calcium and increased IV calcium infusions negates some of the benefits of the subcutaneous administration route of denosumab over IV zoledronic acid.

Sponsor Response:

The statement that heightened monitoring of serum calcium negates some of the benefits of subcutaneous denosumab administration is inaccurate. As patients with cancer and bone metastases often have several reasons for developing electrolyte abnormalities, including hypocalcaemia, oncologists perform regular blood monitoring as part of their care. Appropriate corrective action can, therefore, be taken if hypocalcaemia is detected.

Clinical Summary and Conclusions

Benefit risk assessment

Benefits

The key efficacy results have already been summarized above. In essence, the results from the three pivotal Phase III studies demonstrate a consistent, statistically significant and clinically relevant response for denosumab therapy in terms of reducing further skeletal related events when it is compared to the current standard of care treatment (zoledronic acid) for adult patients with various types of solid tumours involving bone. However, it remains unclear whether harder clinical outcomes such as overall survival and disease progression are impacted significantly by such treatment. In particular, less than 40% of all patients were available for analysis at the conclusion of each pivotal study and the main reason for discontinuation from treatment was death or increasing illness due to other malignancy related manifestations. Therefore, the magnitude of potential benefit is of modest clinical effect at present.

The sponsor proposes a rationale for the selection of the commercially requested dose of denosumab 120 mg SC every 4 weeks but there are limitations to this posology which are outlined in the *Pharmacology* section of this report. In the clinical evaluator's opinion, the dose of denosumab investigated in the Phase III studies and being requested by the sponsor for licensing has not been rigorously justified by the preceding trials. This was considered as a deficiency of the denosumab clinical development program in malignancy.

Risks

The key safety results have already been summarised. In summary, the data shows that denosumab treatment is generally well tolerated and has a comparable safety profile in short term follow up compared to background standard of care treatment for adult patients with malignancy involving bone. Several significant potential safety concerns are evident which include risk of infection (particularly, skin and lower respiratory tract infections leading to hospitalization), osteonecrosis of the jaw and hypocalcaemia. Although these adverse events only appear to affect a small proportion of patients overall, their occurrence would be significant in the majority of those individuals affected. Other potential risks for denosumab use in subjects with malignancy which require ongoing investigation and vigilance include reduced overall survival in patients with multiple myeloma, hypersensitivity reactions and the development of cataracts in men with prostate cancer undergoing androgen deprivation therapy.

Safety Specification

The sponsor provided a Risk Management Plan version 1.0 (dated May 2010) which summarises the important identified and potential safety concerns recognized thus far in the denosumab for malignancy study program. The document has no deficiencies in terms of content. The pharmacovigilance plan outlines routine expected practices included monthly reviews of spontaneously reported adverse events from various established databases as a means of signal detection, review of all suspected cases of serious adverse events, the provision of periodic safety updates to regulatory authorities and the prompt notification of potential serious and/or unexpected adverse events to healthcare professionals. In addition, the product information and labelling should refer to all of these safety matters. The RMP also acknowledges and outlines the rationale as to why specific populations were excluded from the clinical trials.

Balance

There is a need for additional therapeutic options in adult patients with malignancy involving bone and the benefit risk assessment of adding denosumab to the current standard of care is favourable for most patients with solid tumours who are at high risk of further skeletal events. However, given there is substantial uncertainty about the potential benefit for individuals with multiple myeloma, the evaluator would not recommend the licensing of denosumab for this population at this time point based on the submitted data. The sponsor should be encouraged to perform further clinical trials in multiple myeloma patients. The data demonstrates a modest efficacy outcome (prevention of further SRE) but harder clinical outcomes such as changes in disease progression and overall survival (or even analgesic use) has not been demonstrated. Furthermore, some rare but significant safety outcomes (such as ONJ, certain infections requiring hospitalisation and hypocalcaemia) appear to occur in a number of treated patients which will require ongoing pharmacovigilance if the drug is approved for broader use in the Australian community.

Conclusions

The clinical evaluator **recommended** acceptance of the sponsor's proposed indication for denosumab in adult patients with malignancy involving bone as the overall benefit risk balance from the current dataset is in favour of denosumab. However, the sponsor's proposed indication needs to be refined so that it is clear that an indication for patients with multiple myeloma is not recommended. Hence, it was proposed that the indication wording be changed to "*Prevention of skeletal related events in adult patients with bone metastases from solid tumours*". This would also make the approved Australian indication consistent with that approved by the FDA in November 2010. Denosumab appears to have modest efficacy in reducing further skeletal related events that is at least comparable to the current standard of care (zoledronic acid) but both therapies fail to significantly alter harder clinical outcomes such as overall survival.

Conditions for registration

If marketing approval is granted, then wording changes to the proposed indication are needed to more accurately define the patient population that derived clinical benefit in the trials (adult patients with bone metastases from solid tumours). In addition, the sponsor should be asked to provide regular updates (at least annual intervals) to their Risk Management Plan (version 1.0 developed for the European market). The proposed global prospective observational long term safety and pregnancy registries should be a condition of registration.

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

The Ongoing Safety Concerns as specified by the sponsor are summarised in Table 39 below.

Table 39. Summary of Ongoing Safety Concerns.

Identified Risks	Hypocalcemia, osteonecrosis of the jaw, and skin infection leading to hospitalisation
Potential Risks	Infection, hypersensitivity reactions, cardiovascular events, malignancy, overall survival in multiple myeloma, immunogenicity, and cataracts in men with prostate cancer undergoing androgen deprivation therapy
Missing Information	Pregnant and lactating subjects, paediatric subjects, subjects with hepatic impairment

OPR evaluator comment:

Routine pharmacovigilance[35] is proposed by the sponsor to monitor ongoing safety concerns associated with denosumab.

Pursuant to the evaluation of the clinical aspects, was recommended that the above summary of the Ongoing Safety Concerns was considered acceptable. However, it was recommended to the Delegate that the sponsor include the risk of hypocalcaemia in patients with severe renal insufficiency in the ongoing safety concerns that was identified in the Xgeva submission package to the FDA.

Summary of Recommendations

The OPR provides these recommendations in the context that the submitted RMP was supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; and the submitted European Union (EU) RMP is applicable without modification in Australia unless so qualified:

It was recommended to The Delegate that the sponsor:

[35] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

1. *Submit further details of the pregnancy and lactation surveillance programs. That is, will these programs be available in Australia? If so, how will they be implemented and effectiveness evaluated? This information will enable the evaluator to determine the relevance and appropriateness of these programs in Australia.*

Sponsor Response:

Amgen's Pregnancy and Lactation Surveillance programs are active in Australia. Amgen recognizes the importance of proactively and continuously assessing the risk:benefit profile of its products when used by pregnant and lactating women and of communicating this information to healthcare providers, patients, and regulatory agencies. To facilitate such an assessment, Amgen has constructed and implemented the Pregnancy Surveillance Program (PSP) and the Lactation Surveillance Program (LSP), which are robust systems of data collection, management, analysis, and reporting.

The PSP is a global program that gathers data for all Amgen pipeline and marketed products about pregnancy in women who have had exposure to an Amgen product prior to conception or during pregnancy. Information is also gathered when a male sexual partner of a pregnant woman has been exposed to an Amgen product prior to conception, at the time of conception, or during the pregnancy. Clinically relevant human data are collected from the PSP. These data ultimately help inform healthcare providers and patients who are pregnant or are considering pregnancy about the potential effects of an Amgen product on pregnancy and birth outcomes. The program monitors pregnant women who are exposed to denosumab for any indication during pregnancy and/or within the 6 months prior to last menstrual period. Pregnancy and birth outcomes are obtained. In addition, each participating mother will be asked to submit medical records for the infant once it reaches 12 months of age, local regulations and feasibility permitting. Aggregate data obtained from the program will be assessed and analyzed for inclusion in the Pregnancy section of the Periodic Safety Update Report (PSUR).

Like the PSP, the LSP is a global program for all Amgen pipeline and marketed products that gathers information about lactation during exposure to an Amgen product. Amgen encourages participation of all breast feeding women who have concomitantly received denosumab for any indication in the LSP. Breast-fed infants of participating mothers will be followed up through up to 1 year of age. All aggregate data obtained from the program will be assessed and analysed for inclusion in the Lactation section of the PSUR.

· The effectiveness of both of these programs will be evaluated in a number of ways:

· Assessing the percentage of enrolled patients who provide outcomes at prespecified timepoints;

· Measuring the amount of time between adverse event occurrence and reporting;

· Tracking the number of enrolled patients who fail to provide consent to follow-up or release of medical records; and

· Calculating the proportion of enrolled patients who are lost to follow up before a critical outcome (ie, pregnancy and/or birth outcome) is provided to Amgen.

In addition, Amgen is proposing to update the Product Information (PI) and Consumer Medicine Information (CMI) to include the following statements:

Product Information (PI)

Encourage women who become pregnant during Xgeva treatment to enrol in Amgen's Pregnancy Surveillance Program. Enrolment may be arranged by telephoning Amgen's Medical Information line on 1800 803 638 (freecall within Australia).

Encourage women who are nursing during Xgeva treatment to enrol in Amgen's Lactation Surveillance Program. Enrolment may be arranged by telephoning Amgen's Medical Information line on 1800 803 638 (freecall within Australia).

Consumer Medicine Information (CMI)

Tell your doctor if you become pregnant during treatment with Xgevaä or within 6 months of your last dose. Telephone Amgen's Medical Information line on 1800 803 638 (freecall within Australia) to enrol in Amgen's Pregnancy Surveillance program.

If you are breast-feeding during treatment with Xgevaä , telephone Amgen's Medical Information line on 1800 803 638 (freecall within Australia) to enrol in Amgen's Lactation Surveillance program.

2. *Address the unexpected risk of hypocalcaemia in patients with severe renal insufficiency in the risk management plan with appropriate pharmacovigilance and risk minimisation activities.*

Sponsor Response:

The risk of hypocalcemia in patients with severe renal insufficiency is currently addressed by risk communication and minimization through product labelling in the Precautions section of the current PI and in the CMI as follows:

PI

Vitamin supplementation and hypocalcaemia

Pre-existing hypocalcaemia must be corrected prior to initiating therapy with Xgeva. Supplementation with calcium and vitamin D is required in all patients unless hypercalcaemia is present. If hypocalcaemia occurs while receiving Xgeva, additional short term calcium supplementation may be necessary.

Use in Renal Impairment

In a study of 55 patients without advanced cancer, but with varying degrees of renal function, patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis were at greater risk of developing hypocalcaemia. Adequate intake of calcium and vitamin D is important in patients with severe renal impairment or receiving dialysis (see PRECAUTIONS, Vitamin Supplementation and Hypocalcaemia).

CMI

Before you are given it

Tell your doctor if:

you have or have had severe kidney problems, kidney failure or have needed dialysis, which may increase your chance of getting low blood calcium if you do not take calcium supplements.

With respect to pharmacovigilance, in addition to routine surveillance, the risk of hypocalcemia and severe renal impairment will be addressed by proactive surveillance through collection of safety information in a planned clinical study (Study 20101361).

This is a phase 1 study to evaluate the pharmacokinetics, pharmacodynamics, and safety (including changes in serum calcium levels) of multiple 120-mg doses of denosumab in subjects with severe renal impairment (ie, CrCl < 30 mL/min) or receiving dialysis; the study is planned to initiate in the year 2011 and results are expected to be available by Q4 2012. A description of Study 20101361 will be added to the sections of the Risk Management Plan (RMP) listed in the table below:

Section or Table	Section or Table Title
Section 1.3.2.4	Patients with Renal, Hepatic, or Cardiac Impairment
Section 2.1.3.2	Additional Activities in Clinical Studies
Table 2-1	Planned Pharmacovigilance Actions for Identified and Potential Risks
Table 2-3	Ongoing and Planned Denosumab Clinical Studies
Table 2-4	Additional Pharmacovigilance Activities – Actions and Milestones
Table 5-1	Summary of Proposed Pharmacovigilance and Risk Minimization Measures for Advanced Cancer Settings

3. *Provide clarification about the possibility of medication errors with the proposed 120 mg dose from a 70 mg/ml vial and also how this medication error would be appropriately addressed. [A 120 mg dose from a 70 mg/ml vial requires the administrator to draw up 1.7ml which may increase the risk of a medication error.]*

Sponsor Response:

Amgen considers the possibility of this type of medication error with the proposed 120 mg dose form to be low. As stated in the Australian PI, each Xgeva vial contains a "deliverable dose of 120 mg denosumab in 1.7 mL of solution (70 mg/mL)." The recommended dose of Xgeva is 120 mg administered as a single subcutaneous injection of once every 4 weeks, and the dosage and administration section of the label provides clear instructions to "inject the entire contents of the vial."

Denosumab 120 mg (70 mg/mL) vials are filled to ensure that not less than the labeled quantity of product is delivered. The fill volume and concentration are controlled via in-process controls and specifications during the manufacturing process to assure that each vial contains a deliverable quantity of 120 mg.

Amgen will routinely monitor and assess all postmarketing medication error reports, which will be classified as important medical events and reported in PSURs.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There were no objections to registration of the new strength of the product on chemistry, manufacturing or quality control grounds.

Nonclinical data

There are no nonclinical objections to registration. In the current application the sponsor provided some new preclinical data, mainly studies relating to primary pharmacology, and studies of tooth eruption and bone development in neonatal rats. The primary pharmacology studies provided evidence of denosumab efficacy, mainly in osteolytic tumours.

The previously evaluated repeat dose toxicity studies, conducted in monkeys, were adequate to support the safety of the proposed higher dose for the new indication.

Clinical

The clinical evaluator has recommended approval of the application.

Pharmacokinetics (PK)

Four studies were included in the submission that examined the PK of denosumab in patients with cancer. In addition, a population PK analysis examined PK in a heterogeneous group of subjects including patients with cancer. Trough concentrations were also measured in the three pivotal randomised controlled trials submitted with the current Australian application.

The PK of denosumab in patients with cancer were generally comparable with those seen in previous studies. C_{max} increased in a dose proportional manner. AUC increased in a dose proportional manner at the proposed dose range (>1 mg/kg). Median T_{max} occurred at 14-18 days with 4-weekly dosing and the half-life ranged from 25 – 35 days. Clearance was generally consistent across various tumour types, with the possible exception of multiple myeloma, where clearance appeared to be increased. With the proposed fixed dose regimen, systemic exposure decreased with increasing weight.

Cross trial comparisons suggested that the PK of denosumab were unchanged in patients who had received prior bisphosphonate treatment and were similar in patients receiving chemotherapy compared to those receiving hormonal therapy. The clinical evaluator commented that significant PK drug interactions were unlikely to exist.

Pharmacodynamics

Several studies included in the submission examined the effect of denosumab on urinary N-telopeptide (NTX), a marker of bone resorption. Treatment with denosumab was associated with decreases in urinary NTX. A dose-response effect was observed for doses up to 1 mg/kg.

The dose selected for the Phase III trials was justified on pharmacodynamic grounds.

Efficacy

Evidence for efficacy comes from three randomised, double-blind, and parallel group design trials which compared denosumab with zoledronic acid. The three trials have been published:

- Study 2005-0103 enrolled subjects with hormone refractory prostate cancer[36];
- Study 2005-0136 enrolled subjects with breast cancer[37];

[36] Fizaz K. *et al* (2011). Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet* 377: 813‑22

[37] Stopeck A.T. *et al* (2010). Denosumab Compared With Zoledronic Acid for the Treatment of Bone Metastases in Patients With Advanced Breast Cancer: A Randomized, Double-Blind Study. *J Clin Oncol* 28:5132-5139.

- Study 2005-0244 enrolled subjects with solid tumours (other than prostate cancer or breast cancer) or multiple myeloma[38].

In all three studies, patients were required to have at least one bony metastasis (or osteolytic lesion for myeloma) at baseline.

The dose of denosumab used in each of the three trials was 120 mg SC every 4 weeks. The dose of zoledronic acid used in each study was 4 mg IV every 4 weeks. The approved dosage regimen for zoledronic acid in Australia is 4 mg IV **every 3-4** weeks.

The primary endpoint for all three studies was time to first on study skeletal related event (SRE). An SRE was defined as any of the following:

- Pathological fracture;
- Radiation therapy to bone;
- Surgery to bone; or
- Spinal cord compression.

This endpoint has previously been accepted by the Advisory Committee for Prescription medicines (ACPM) and the TGA when approving zoledronic acid.

In all three studies the primary endpoint was tested for non inferiority of denosumab versus zoledronic acid. If non inferiority was demonstrated, superiority of denosumab over zoledronic acid was tested as a secondary endpoint. Another secondary endpoint, time to first *and subsequent* on study SRE measured the cumulative incidence of SREs. A number of exploratory endpoints were also examined.

Results for the three studies were:

- In Study 2005-0103 (prostate cancer) denosumab was shown to be non inferior and superior to zoledronic acid for time to first on study SRE. The absolute reduction in the percentage of patients who experienced an SRE was 4.7% (35.9% versus 40.6%);
- In Study 2005-0136 (breast cancer) denosumab was shown to be non-inferior and superior to zoledronic acid for time to first on study SRE. The absolute reduction in the percentage of patients who experienced an SRE was 5.8% (30.7% versus 36.5%);
- Study 2005-0244 (other solid tumours or multiple myeloma) denosumab was shown to be non-inferior to zoledronic acid for time to first on study SRE. On testing for superiority, the difference between treatments was not statistically significant.

In all three studies there were no significant differences between the two treatments in overall survival or in measures of time to disease progression. However, in Study 2005-0244, a subgroup analysis suggested that patients with myeloma treated with denosumab may have an inferior survival compared to those treated with zoledronic acid.

Safety

In the Phase III studies, a total of 2841 subjects were exposed to denosumab. Of these, 2151 received treatment for > 6 months and 1535 received treatment for > 12 months.

[38] Henry D. H. *et al* (2011). Randomized, Double-Blind Study of Denosumab Versus Zoledronic Acid in the Treatment of Bone Metastases in Patients With Advanced Cancer (Excluding Breast and Prostate Cancer) or Multiple Myeloma. *J Clin Oncol* 29:1125-1132.

Across the three pivotal studies, the overall safety profile of denosumab compared to zoledronic acid in terms of incidence of adverse events is summarised in Table 40.

Table 40. Overall Safety Profile of Denosumab.

	Denosumab	Zoledronic acid
Adverse events (AEs)	96.2 %	96.8 %
Related AEs	29.1 %	33.1 %
Serious AEs	56.3 %	57.1 %
Fatal AEs	28.7 %	29.0 %
Related fatal AEs	0.4 %	0.6 %
Discontinuations due to AEs	12.4 %	13.1 %

These data suggest that the two drugs have comparable overall toxicity.

With respect to individual toxicities, denosumab was associated with an increased incidence of the following:

- Hypocalcaemia (9.3% versus 4.7%), including severe hypocalcaemia (1.4% versus 0.6%);
- Dyspnoea (20.6 % versus 17.9%);
- Hyperhidrosis (2.3% versus 1.3%);
- Osteonecrosis of the jaw (1.8% versus 1.3%);
- Hypersensitivity reactions (5.4% versus 3.8%)

Denosumab was associated with a *reduced* incidence of the following:

- Adverse events indicative of the acute phase reaction commonly seen with zoledronic acid such as pyrexia, bone pain, arthralgia, chills and myalgia;
- Renal toxicity (9.2 versus 11.8%) and renal failure (2.6% versus 3.7%).

Risk Management Plan

The sponsor has provided an RMP which has been found to be acceptable by the TGA's Office of Product Review.

Risk-Benefit Analysis

Overall risk-benefit

The three pivotal studies have demonstrated that denosumab is at least non inferior to zoledronic acid in preventing SREs. In two of the studies, denosumab was superior to zoledronic acid, with a modest improvement in efficacy. The overall safety profile of the two drugs was comparable with some differences in the pattern of individual adverse effects. Denosumab may be associated with an increased incidence of ONJ which is of concern. However it is also associated with a reduced incidence of renal toxicity. Overall the Delegate considered that the data establish that denosumab has a comparable risk-benefit profile to that of zoledronic acid. The Delegate therefore proposed to approve the application.

Use in patients with multiple myeloma

The subgroup analysis of Study 2005-0244 suggested that use of denosumab in patients with myeloma may be associated with a reduced survival compared to patients treated with zoledronic acid. The clinical evaluator has recommended that denosumab should not be approved for use myeloma patients and has noted that a further randomised controlled trial is planned to examine this issue.

In its response to the clinical evaluation the sponsor has agreed to exclude myeloma patients from the proposed indication.

Proposed dosage regimen

The clinical evaluator has questioned the choice of the 120 mg fixed dose regimen on pharmacokinetic and pharmacodynamic grounds, suggesting that a lower dose, adjusted according to patient's weight may have been more appropriate.

The clinical evaluator did not identify this issue as grounds for rejection of the application. The Delegate also did not consider this issue should be a barrier to registration approval, as the selected dose was demonstrated to have a favourable risk benefit profile and there are no clinical data to support an alternative dosage regimen. It is also noted that a fixed dose regimen has already been registered for the current osteoporosis indication.

Proposed action

The Delegate proposed to approve the application. The advice of the ACPM was requested.

Response from Sponsor

Published references cited in this section are listed at the end of the sponsor's response.

1. Sponsor's response to the Nonclinical evaluation

A. The ability of pharmacologic RANKL inhibitors, including RANK-Fc or OPG, to effectively prevent or reduce bone resorption due to high PTHrP levels has also been demonstrated in a number of rodent cancer models. Oyajobi *et al*., (2001) tested whether RANKL inhibition (via RANK-Fc) would prevent hypercalcaemia associated with PTHrP-secreting human lung SCC tumour cells RWGT2.Treatment with RANK-Fc, initiated from the time of tumour inoculation, prevented tumour associated hypercalcaemia and this was associated with significantly decreased osteoclast numbers on bone surfaces. Two studies have analysed the effects of RANKL inhibition using OPG in the C-26colon adenocarcinoma model, in which significant elevations in serum PTHrP was associated with increased osteoclast surface and hypercalcaemia. In the study by Capparelli *et al*., (1999), treatment of mice bearing the C26 tumour with OPG significantly delayed the onset of hypercalcaemia and this response was accompanied by a 99% reduction in osteoclast surface. In the second study (Morony *et al*., 2005) mice with established hypercalcaemia due to C-26 tumours were treated once (i.v.) with 0.2, 1 and 5 mg/kg OPG-Fc resulting in a significant reduction in serum calcium levels within 12 hr, reaching a nadir at 48 hr.Both 1 and 5 mg/kg OPG-Fc normalised serum calcium levels within 48 hours, while each dose of OPG-Fc significantly reduced osteoclast surface relative to tumour-bearing animals 5 days after treatment, however only the 5 mg/kg dose significantly reduced osteoclast surface relative to non-tumour bearing controls.

Several lines of evidence indicate that PTHrP stimulates bone resorption via local increases in RANKL and/or local decreases in OPG, leading to a net increased RANKL signal. One single study reports an incomplete reduction of tumour-associated

osteoclasts in a PTHrP-secreting tumour (HARA tumour model; Tannehilll-Gregg et al., 2006). Given the evidence from multiple studies demonstrating efficacy of RANKL inhibition, Amgen maintains that the lack of efficacy in the HARA model upon treatment with 2.5 mg/kg OPG-Fc (biw) is not due to the general inability of RANKL inhibition to block PTHrP-mediated bone resorption, but rather is likely due to the suboptimal dose/schedule used in the Tannehill-Gregg study. A review of the available nonclinical data suggests that RANKL inhibition would, in fact, be efficacious in a PTHrP-expressing tumour.

B. Published nonclinical studies describe the efficacy of RANKL inhibition on the establishment and progression of osteoblastic tumours (Kiefer *et al* 2004; Zhang *et al* 2003; Yonou *et al* 2004), suggesting that osteoclasts and osteoclast mediated bone resorption can promote tumour growth, even if the resulting phenotype of the bony lesion is osteoblastic. The one study in which RANKL inhibition did not apparently show efficacy in an osteoblastic model had unique experimental design limitations which might preclude the accurate analysis of a bone targeted agent in this particular model.

Taken together, the analysis of RANKL inhibition in rodent models of cancer bone metastasis representing diverse bone lesions (including osteolytic and osteoblastic metastases) provides further support for the notion that inhibition of RANKL and subsequent reduction in osteoclastogenesis may be useful for the treatment of bone metastases across a wide spectrum of bone lesions. Furthermore, integrated clinical data from the three pivotal Phase III studies with denosumab for the prevention of SREs in patients with advanced malignancies involving bone demonstrate a clinically meaningful treatment effect of denosumab, regardless of lesion type at baseline and tumour type of origin.

2. Overall risk-benefit

In the overall risk-benefit assessment of the Delegate's overview and in several places throughout the Clinical Evaluation Report (CER), the effect of denosumab is referred to as 'modest'. Furthermore, the Delegate's overview stated that 'denosumab is at least non-inferior to zoledronic acid' and that 'denosumab has a comparable risk-benefit profile to that of zoledronic acid'. Amgen considers these statements to be inaccurate and potentially misleading.

Denosumab demonstrated clinically meaningful increased effectiveness for preventing or delaying skeletal-related events (SREs) compared with zoledronic acid. This effect was robust and consistent in each of the Phase III studies and in the integrated analysis. Specifically, denosumab demonstrated superiority to zoledronic acid in the treatment of subjects with breast and prostate cancer (Studies 20050136 and 20050103) and non inferiority (trending to superiority) in the treatment of subjects with other solid tumours or multiple myeloma (Study 20050244). Superiority was further supported by the post hoc analysis of Study 20050244 including patients with solid tumours and excluding those with multiple myeloma. As previously stated in our response to the CER, the effects of denosumab are clinically relevant, with a meaningful delay in experiencing a first on study SRE compared with zoledronic acid (not calculable in Study 20050136, 4.2 months in Study 20050244, 3.5 months in Study 20050103, and 8.2 months in the integrated analysis). The delays in experiencing a first SRE are particularly important given the lifespan of patients with advanced cancer, which in these studies was a median of 22 months. The clinical relevance of these results also is illustrated by comparing the effects

of denosumab back to placebo, using data from the zoledronic acid registration studies. This calculation shows that denosumab reduced the risk of developing a first SRE by a large magnitude in each study, compared with placebo (48% in Study 20050136, 40% in Study 20050244, and 44% in Study 20050103).

Furthermore, in the results for the first and subsequent SRE endpoint that assessed the total burden of SREs in these studies, the total number of SREs (excluding events that occurred within a 21-day window between events) was 1360 and 1628 in the denosumab and zoledronic acid groups, respectively, corresponding to a clinically relevant difference of 268 events in these approximately 5700 subjects. If all events are included by removing the 21 day window restriction, the total number of SREs was 1996 and 2422 in the denosumab and zoledronic acid groups, respectively, corresponding to a clinically relevant difference of 426 events in approximately 5700 subjects. The efficacy of denosumab was sustained over time; no attenuation of efficacy over time was observed. Kaplan-Meier estimates and the separation of the Kaplan- Meier curves demonstrate that the greater effect of denosumab compared with zoledronic acid on reducing SREs was seen early and was sustained over the 2.5 year period. No inconsistency in efficacy was observed across components of the composite SRE endpoint; the numbers of subjects and events were lower for each SRE component in the denosumab group compared with the zoledronic acid group in the integrated analyses.

The Delegate also described the toxicity of the denosumab and zoledronic acid to be 'comparable', suggesting that the risk of both agents is similar. However, results from the pivotal clinical studies demonstrate that while both agents are associated with an increased risk of hypocalcemia and ONJ, denosumab is not associated with important treatment limiting toxicities that are associated with zoledronic acid, including renal toxicity and acute phase reactions.

A higher incidence of hypocalcemia adverse events was observed with denosumab compared with zoledronic acid (9.6% and 5.0%, respectively). These events were mainly non serious, transient and resolved either spontaneously or with calcium supplementation. ONJ was observed infrequently with both denosumab and zoledronic acid (1.8% and 1.3%, respectively; p = 0.1343), with the clinical characteristics of these cases being similar in each group. Both of these events can be adequately managed with appropriate preventive and corrective measures.

Minimizing exposure to drugs that may increase the risk of nephrotoxicity is an important consideration in the treatment of patients with advanced cancer. Renal complications occur frequently in these patients (approximately 50% to 60%) for a variety of reasons, including from the use of nephrotoxic chemotherapies (such as platinum agents) and antibiotics (such as aminoglycosides), and from cancer related disease processes such as urinary obstruction (Launay-Vacher *et al*, 2008; Cimino *et al*, 1987; Ries and Klastersky, 1986; Oh *et al*, 2007); these result in a continued risk and underlying rate of renal impairment. Antiresorptive treatment with intravenous (IV) bisphosphonates further exacerbates the risk for and rate of renal impairment in these patients (Zometa, 2009; Aredia, 2008; Chang *et al*, 2003), thereby increasing the complexity of their care. A need exists to provide a safe and effective therapy in patients with severe renal impairment, for whom IV bisphosphonates are not recommended for use and the risk for developing SREs goes untreated (Zometa, 2009, Aredia, 2008). Also, acute phase reactions are a well known side effect of zoledronic acid (Zometa, 2009). At times, these reactions can be severe and treatment-limiting due to a patient's reluctance to continue treatment (Diel *et al*, 2007, Olson and Van Poznak, 2007).

Additionally, the subcutaneous route of administration of denosumab does not require the venous access or extended infusion times that can limit the use of zoledronic acid, particularly in patients who do not have venous access or do not have ready access to facilities capable of administering IV therapy (Barrett-Lee *et al*, 2007).

Thus, the demonstrated superior efficacy, elimination of treatment limiting toxicities, and route of administration of denosumab shifts the risk benefit balance in its favour.

Amgen's position regarding the demonstration of denosumab's clinically meaningful superiority is further reinforced by:

i) the US FDA's decision to grant priority review status for denosumab, a process reserved for drugs that offer major advances in treatment or provide a treatment where no adequate therapy exists; and

ii) the Committee for Medicinal Products for Human Use (CHMP) recommended to grant denosumab an additional year of data and market exclusivity in the European Union, as the risk/benefit balance for Xgeva is considered to be positive and as there is a significant benefit of the product in comparison with existing therapies in terms of prolonged time to first SRE, less nephrotoxicity, and a simpler mode of administration.

In summary, the results of the pivotal Phase III studies demonstrate clinically relevant delays in the time to first SRE, reductions in the overall burden of SREs and superior efficacy of denosumab compared with zoledronic acid. Denosumab offers a significant advance in efficacy for the treatment of patients with bone metastases from solid tumours to prevent or delay SREs, compared with the current standard of care, zoledronic acid. This is evidenced by: a reduction in SREs of 17% compared with the most effective available therapy (zoledronic acid), a reduction in SREs of approximately 40% to 48% compared with placebo, the ability to treat patients who are currently not eligible to receive existing bone targeted therapy due to severe renal impairment, and the ability to dose using a single, SC injection that does not require venous access and does not requirerenal monitoring. These results demonstrate clinically meaningful superiority of denosumab, which is neither 'modest' nor 'non-inferior'.

3. Proposed dosage regimen

Amgen agrees with the Delegate's assessment that the 120 mg fixed dose regimen has demonstrated a favourable risk-benefit profile. The collective pharmacokinetic, pharmacodynamic (that is, bone resorption marker urine N-telopeptide corrected for urine creatinine [uNTx/Cr]), and efficacy data demonstrate that the proposed fixed-dose regimen accounts for the modest effect of body weight on pharmacokinetics and is thus appropriate, while there are no clinical data supporting the use of a weight-based dose regimen. This is consistent with the approved fixed dose regimen for Prolia (denosumab), for the treatment of postmenopausal osteoporosis.

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Zometa (zoledronic acid) [United States Prescribing Information.] East Hanover, NJ: Novartis Pharmaceutical Corporation: 2009(b).

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and The Delegate's overview, as well as the sponsor's response to these documents, agreed with The Delegate's proposal.

In expressing its view that this submission for denosumab (Xgeva) solution 70 mg/mL was suitable to be considered for approval, the ACPM considered the following matters:

It was noted that there were no quality control, manufacturing, chemistry or nonclinical issues that remain unresolved.

Efficacy: The three pivotal studies have demonstrated that denosumab is at least non inferior to zoledronic acid in preventing skeletal related events. In two of the studies, denosumab was superior to zoledronic acid, with a modest improvement in efficacy.

Safety: The overall safety profile of the two drugs was comparable with some differences in the pattern of individual adverse effects. The apparent increased risk of osteonecrosis of the jaw is of concern and requires monitoring.

It was noted that the sponsor has agreed to exclude patients with multiple myeloma following the subgroup analysis of Study 2005-0244 which suggested that use of denosumab may be associated with a reduced survival compared to patients treated with zoledronic acid.

Although dosing based on weight may reduce toxicity, the trials demonstrated a favourable risk benefit profile for the fixed dose and there are no clinical data to support an alternative dosage regimen.

The use of a separate trade name and Product Information document for two strengths is considered acceptable on the grounds of making a clear distinction between doses and may prevent dispensing mistakes.

The ACPM, taking into account the submitted evidence of pharmaceutical quality, safety and efficacy, considered there is a favourable benefit risk profile for this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Xgeva Solution for Injection vial containing denosumab *rch* 70 mg/mL for subcutaneous injection, indicated for:

Prevention of skeletal related events in patients with bone metastases from solid tumours.

Specific Conditions applying to these therapeutic goods:

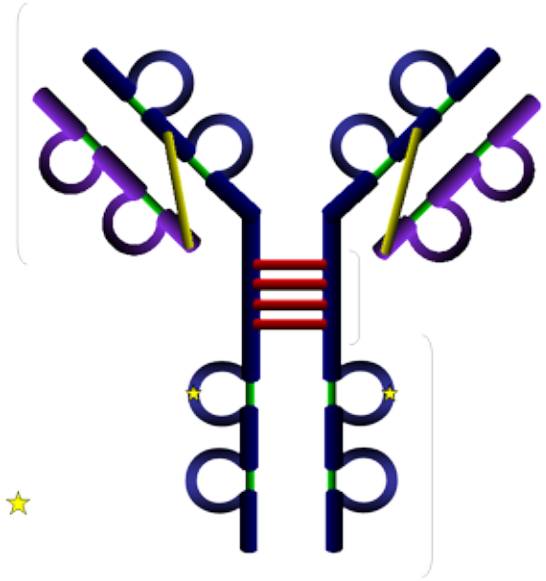
1. It is a condition of registration that you implement in Australia the denosumab *rch* RMP version 1.0, dated 7 May 2010, including your response to the RMP evaluation dated 10 June 2011 and any future updates, as agreed with the TGA and its Office of Product Review.
2. It is a condition of registration that the first five independent batches of Xgeva imported into Australia are not released for sale until samples and/or the manufacture's release data have been assessed and endorsed for release by the TGA Office of Laboratories and Scientific Services (OLSS).

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

NAME OF THE MEDICINE

XGEVA® is the Amgen Inc. trademark for denosumab (rch).



DESCRIPTION

Denosumab is a fully human IgG2 monoclonal antibody with high affinity and specificity for RANK ligand (RANKL). Denosumab has an approximate molecular weight of 147 kDa and is produced in genetically engineered mammalian (Chinese Hamster Ovary, CHO) cells.

CAS number: 615258-40-7

Xgeva is a sterile, preservative-free, clear, colourless to slightly yellow solution. The solution may contain trace amounts of translucent to white proteinaceous particles. Each single-use vial contains a deliverable dose of 120 mg denosumab, 78 mg sorbitol, 1.8 mg acetate, and sodium hydroxide for adjusting to pH 5.2, in Water for Injection (USP, PhEur, JP).

PHARMACOLOGY

Mechanism of Action

RANKL exists as a transmembrane or soluble protein. RANKL is essential for the formation, function and survival of osteoclasts, the sole cell type responsible for bone resorption. Increased osteoclast activity, stimulated by RANK ligand, is a key mediator of bone destruction in bone disease in metastatic tumours and multiple myeloma. Denosumab binds with high affinity and specificity to RANKL, preventing RANKL from activating its only receptor, RANK, on the surface of osteoclasts and their precursors. Prevention of RANK ligand-RANK interaction results in reduced osteoclast numbers and function, and thereby decreases bone resorption and cancer-induced bone destruction.

RANKL inhibition resulted in reduced bone lesions and delayed formation of *de novo* bone metastases in some nonclinical models. RANKL inhibition reduced skeletal tumour growth and this effect was additive when combined with other anticancer therapies.

Pharmacodynamics

In a phase 2 study of IV-bisphosphonate naïve patients with breast cancer and bone metastases, subcutaneous (SC) doses of Xgeva 120 mg every 4 weeks (Q4W) caused a rapid reduction in markers of bone resorption (uNTx/creatinine, serum CTx) with median reduction of 82% for uNTx/Cr within 1 week. Reductions in bone resorption markers were maintained, with median uNTx/Cr reductions of 74% to 82% from weeks 2 to 25 of continued 120 mg Q4W dosing. Median reduction of approximately 80% in uNTx/Cr from baseline after 3 months of treatment were also observed across 2075 Xgeva-treated advanced cancer patients (breast, prostate, multiple myeloma or other solid tumours) naïve to IV-bisphosphonate in the phase 3 clinical trials.

Similarly, in a phase 2 study of patients with advanced malignancies and bone metastases (including subjects with multiple myeloma and bone disease) who were receiving intravenous bisphosphonate therapy, yet had uNTx/Cr levels > 50 nM/mM, SC dosing of Xgeva administered either every 4 weeks or every 12 weeks caused an approximate 80% reduction in uNTx/Cr from baseline after 3 and 6 months of treatment. Overall, 97% of patients in the Xgeva groups had at least one uNTx/Cr value < 50 nM/mM up to week 25 of the study.

Pharmacokinetics

Following subcutaneous administration, bioavailability was 62% and denosumab displayed non-linear pharmacokinetics with dose over a wide dose range, but approximately dose-proportional increases in exposure for doses of 60 mg (or 1 mg/kg) and higher.

With multiple doses of 120 mg every 4 weeks (Q4W) an approximate 2-fold accumulation in serum denosumab concentrations was observed and steady-state was achieved by 6 months, consistent with time-independent pharmacokinetics. At steady-state, the mean serum trough concentration was 20.6 µg/mL (range: 0.456 to 56.9 µg/mL). In subjects who discontinued 120 mg every 4 weeks, the mean half-life was 28 days (range: 14 to 55 days).

A population pharmacokinetic analysis showed no notable difference in pharmacokinetics with age (18 to 87 years), race, body weight (36 to 174 kg), or across patients with solid tumours. Denosumab pharmacokinetics and pharmacodynamics were not affected by the formation of binding antibodies to denosumab and were similar in men and women.

The pharmacokinetics and pharmacodynamics of denosumab were similar in patients transitioning from IV bisphosphonate therapy.

Denosumab is composed solely of amino acids and carbohydrates as native immunoglobulin and is unlikely to be eliminated via hepatic metabolic mechanisms. Its metabolism and elimination are expected to follow the immunoglobulin clearance pathways, resulting in degradation to small peptides and individual amino acids.

Special populations

Elderly

The pharmacokinetics of denosumab were not affected by age (18 to 87 years).

Paediatric

The pharmacokinetic profile has not been assessed in those < 18 years.

Impaired hepatic function

The pharmacokinetic profile has not been assessed in patients with impaired hepatic function.

Impaired renal function
In a study of 55 patients without advanced malignancies but with varying degrees of renal function, including patients on dialysis, the degree of renal impairment had no effect on the pharmacokinetics and pharmacodynamics of denosumab. Dose adjustment for renal impairment is not necessary.

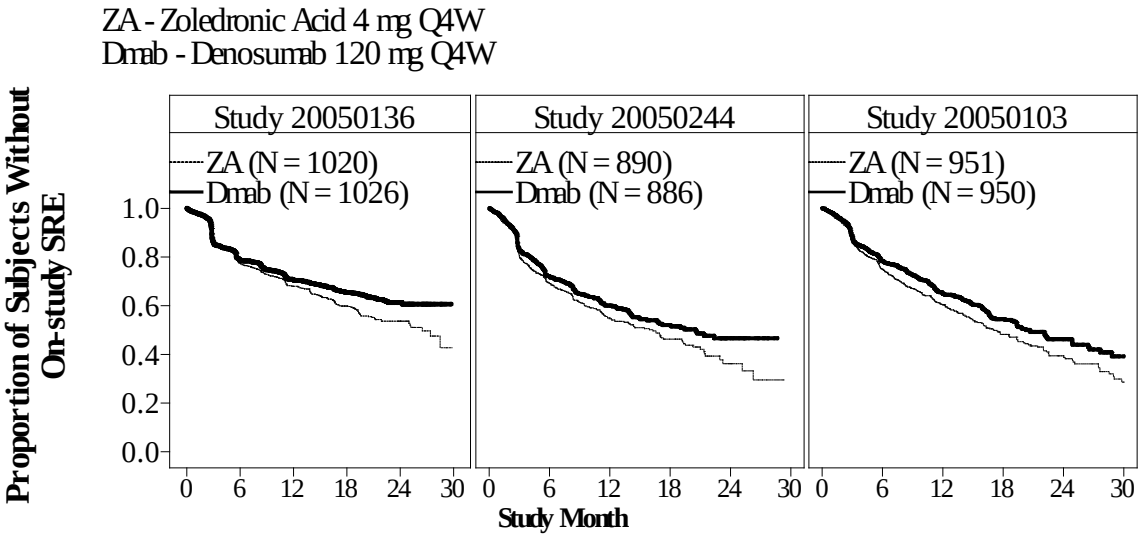
Immunogenicity
In clinical studies, no neutralising antibodies for denosumab have been observed. Using a sensitive immunoassay, < 1% of patients treated with denosumab for up to 3 years tested positive for non neutralising binding antibodies with no evidence of altered pharmacokinetics, toxicity, or clinical response.

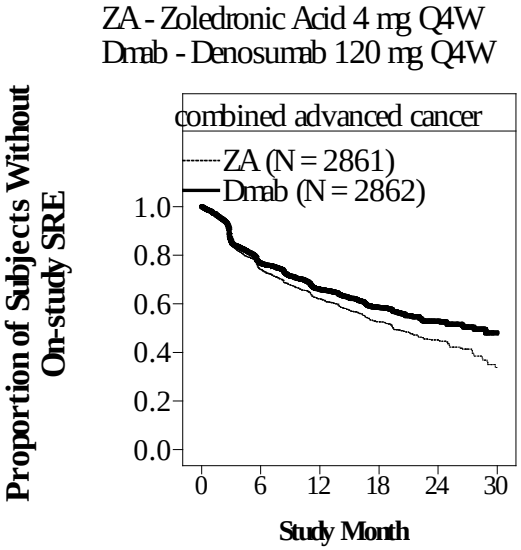
CLINICAL TRIALS

Clinical efficacy in patients with advanced malignancies involving bone
Efficacy and safety of 120 mg Xgeva subcutaneously every 4 weeks or 4 mg zoledronic acid (dose-adjusted for reduced renal function) IV every 4 weeks were compared in three randomised, double blind, active controlled studies, in IV-bisphosphonates naïve patients with advanced malignancies involving bone. A total of 2,046 adults with breast cancer with at least one bone metastasis (Study 20050136), 1,776 adults with other solid tumours (including non-small cell lung cancer, renal cell cancer, colorectal cancer, small cell lung cancer, bladder cancer, head and neck cancer, gastrointestinal/genitourinary cancer and others, excluding breast and prostate cancer) with at least one bone metastasis or multiple myeloma (Study 20050244), and 1,901 men with castrate-resistant prostate cancer with at least one bone metastasis (Study 20050103) were included. The primary and secondary endpoints evaluated the occurrence of one or more skeletal related events (SREs) defined as any of the following: pathologic fracture, radiation therapy to bone, surgery to bone or spinal cord compression.

Xgeva reduced the risk of developing a SRE, or developing multiple SREs (first and subsequent) in patients with advanced malignancies involving bone (see Figure 1 and Table 1).

Figure 1. Kaplan-Meier plot of time to first on-study SRE





N = number of subjects randomised

Table 1: Efficacy results in patients with advanced malignancies involving bone

	Study 20050136 breast cancer		Study 20050244 other solid tumours or multiple myeloma		Study 20050103 prostate cancer		Combined advanced cancer	
	Xgeva	zoledronic acid	Xgeva	zoledronic acid	Xgeva	zoledronic acid	Xgeva	zoledronic acid
N	1026	1020	886	890	950	951	2862	2861
First SRE								
Median time (months)	NR	26.4	20.6	16.3	20.7	17.1	27.6	19.4
Diff in median time (months)	NA		4.2		3.5		8.2	
Hazard ratio (95% CI)	0.82 (0.71, 0.95)		0.84 (0.71, 0.98)		0.82 (0.71, 0.95)		0.83 (0.76, 0.90)	
Risk reduction (%)	18		16		18		17	
Non-inferiority p-value	< 0.0001†		0.0007†		0.0002†		< 0.0001	
Superiority p-value	0.0101†		0.0619†		0.0085†		< 0.0001	
Proportion of subjects (%)	30.7	36.5	31.4	36.3	35.9	40.6	32.6	37.8
First and subsequent SRE*								
Mean number/ patient	0.46	0.60	0.44	0.49	0.52	0.61	0.48	0.57
Rate ratio (95% CI)	0.77 (0.66, 0.89)		0.90 (0.77, 1.04)		0.82 (0.71, 0.94)		0.82 (0.75, 0.89)	
Risk reduction (%)	23		10		18		18	
Superiority p-value	0.0012†		0.1447†		0.0085†		< 0.0001	
SMR per year	0.45	0.58	0.86	1.04	0.79	0.83	0.69	0.81
First Radiation to Bone								
Median time (months)	NR	NR	NR	NR	NR	28.6	NR	33.2
Hazard ratio (95% CI)	0.74 (0.59, 0.94)		0.78 (0.63, 0.97)		0.78 (0.66, 0.94)		0.77 [0.69, 0.87]	
Risk reduction (%)	26		22		22		23	
Superiority p-value	0.0121		0.0256		0.0071		< 0.0001	

NR = not reached; NA = not available; SRE = skeletal related event; SMR = skeletal morbidity rate: defined as the ratio of the number of occurrence of any SRE for a subject, allowing 1 event per assessing period (eg, 3 weeks), divided by the subject's time at risk; †Adjusted p-values are presented for studies 1, 2 and 3 (first SRE and first and subsequent SRE endpoints); *Accounts for all skeletal events over time; only events occurring ≥ 21 days after the previous event are counted.

In a post-hoc analysis of Study 20050244 (including solid tumours, excluding multiple myeloma), Xgeva reduced the risk of developing a SRE by 19% (p = 0.0168) and developing multiple SREs by 15% (p = 0.0479) compared with zoledronic acid with the median time to first SRE delayed by 6 months.

Disease progression and overall survival

Disease progression was similar between Xgeva and zoledronic acid in all three studies and in the pre-specified analysis of all three-studies combined.

In all three studies overall survival was balanced between Xgeva and zoledronic acid in patients with advanced malignancies involving bone: patients with breast cancer (hazard ratio [95% CI] was 0.95

[0.81, 1.11]), patients with prostate cancer (hazard ratio [95% CI] was 1.03 [0.91, 1.17]), and patients with other solid tumours or multiple myeloma (hazard ratio [95% CI] was 0.95 [0.83, 1.08]. A post-hoc analysis in Study 20050244 (patients with other solid tumours or multiple myeloma) examined overall survival for the three tumour types used for stratification (non-small cell lung cancer, multiple myeloma, and other). Overall survival was longer for Xgeva in non-small cell lung cancer (hazard ratio [95% CI] of 0.79 [0.65, 0.95]; n = 702) and longer for zoledronic acid in multiple myeloma (hazard ratio [95% CI] of 2.26 [1.13, 4.50]; n = 180) and similar between the Xgeva and zoledronic acid groups in other tumour types (hazard ratio [95% CI] of 1.08 [0.90, 1.30]; n=894). This study did not control for prognostic factors and anti-neoplastic treatments. In a combined pre-specified analysis from all three studies, overall survival was similar between Xgeva and zoledronic acid (hazard ratio [95% CI] of 0.99 [0.91, 1.07]).

INDICATIONS

Prevention of skeletal related events in patients with bone metastases from solid tumours.

CONTRAINDICATIONS

Hypersensitivity to the active substance, to CHO-derived proteins or to any of the excipients (see DESCRIPTION).

PRECAUTIONS

Vitamin Supplementation and Hypocalcaemia

Pre-existing hypocalcaemia must be corrected prior to initiating therapy with Xgeva.

Supplementation with calcium and vitamin D is required in all patients unless hypercalcaemia is present.

If hypocalcaemia occurs while receiving Xgeva, additional short term calcium supplementation may be necessary.

Use in Multiple Myeloma

The currently available clinical trial data do not support the use of Xgeva in patients with multiple myeloma (see CLINICAL TRIALS).

Use in Renal Impairment

No dose adjustment is necessary in patients with renal impairment.

In a study of 55 patients without advanced cancer, but with varying degrees of renal function, patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis were at greater risk of developing hypocalcaemia. Adequate intake of calcium and vitamin D is important in patients with severe renal impairment or receiving dialysis (see PRECAUTIONS, Vitamin Supplementation and Hypocalcaemia).

Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) was reported in patients treated with denosumab, predominantly in patients with advanced malignancies involving bone.

Patients who developed ONJ in clinical studies generally had known risk factors for ONJ, including invasive dental procedures (e.g., tooth extraction, dental implants, oral surgery), poor oral hygiene or other pre-existing dental disease, advanced malignancies, or concomitant therapies (e.g.,

chemotherapy, corticosteroids, angiogenesis inhibitors). An oral examination should be performed by the prescriber prior to initiation of Xgeva treatment and a dental examination with appropriate preventive dentistry should be considered prior to treatment with Xgeva. While on treatment, these patients should avoid invasive dental procedures if possible.

Good oral hygiene practices should be maintained during treatment with Xgeva. Patients who are suspected of having or who develop ONJ while on Xgeva should receive care by a dentist or an oral surgeon. If ONJ occurs during treatment with Xgeva, use clinical judgment and guide the management plan of each patient based on individual benefit-risk evaluation.

Drugs with Same Active Ingredient

Xgeva contains the same active ingredient found in Prolia® (denosumab), used for the treatment of postmenopausal osteoporosis. Patients being treated with Xgeva should not be treated with Prolia® concomitantly.

Skin Infections

An imbalance of skin infections leading to hospitalisation was reported in a single placebo-controlled study of postmenopausal women with osteoporosis treated with Prolia (denosumab 60 mg every 6 months). In clinical trials in patients with advanced malignancies involving bone, skin infections leading to hospitalisation (predominantly cellulitis) were reported (see ADVERSE EFFECTS). Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis.

Use in the Elderly

Of the total number of patients in clinical studies in patients with advanced cancer, 1260 patients (44.4%) treated with Xgeva were ≥ 65 years old. No overall differences in safety or efficacy were observed between these patients and younger patients.

Paediatric Use

The safety and efficacy of Xgeva in paediatric patients have not been established. Xgeva is not recommended for use in paediatric patients. Adolescent primates had abnormal growth plates when administered denosumab at doses of 10 mg/kg and higher, which resulted in exposures up to 2.8 times those observed in adult humans dosed at 120 mg subcutaneously every 4 weeks based on AUC. In neonatal rats, inhibition of RANKL (target of denosumab therapy) with a construct of osteoprotegerin bound to Fc (OPG-Fc) was associated with inhibition of bone growth and tooth eruption and lower body weight gain. These changes were partially reversible when dosing of RANKL inhibitor was discontinued. Therefore, treatment with denosumab may impair bone growth in children with open growth plates and may inhibit eruption of dentition.

Effects on Fertility

No data are available on the effect of denosumab on human fertility. Denosumab had no effect on female fertility or male reproductive organs or sperm motility in cynomolgus monkeys at subcutaneous doses up to 12.5 mg/kg/week (females) or 50 mg/kg/month (males), yielding exposures that were approximately 15-fold higher than the human exposure at 120mg subcutaneous administered once every month.

Use in Pregnancy

Pregnancy Category: D

There are no adequate and well-controlled studies of Xgeva in pregnant women. Xgeva is not recommended for use during pregnancy. Encourage women who become pregnant during Xgeva

treatment to enrol in Amgen's Pregnancy Surveillance Program. Enrolment may be arranged by telephoning Amgen's Medical Information line on 1800 803 638 (freecall within Australia).

Developmental toxicity studies have been performed with denosumab in cynomolgus monkeys at subcutaneous doses up to 12.5 mg/kg/week, yielding exposures up to 9.5 fold higher than the human exposure. No evidence of harm to the foetus was observed. Preclinical studies in RANK/RANKL-knockout mice suggest absence of RANKL could interfere with the development of lymph nodes in the foetus; the potential for adverse effects on lymph node development was not examined in studies with denosumab in monkeys. Knockout mice lacking RANK or RANKL also exhibited decreased body weight, reduced bone growth and a lack of tooth eruption. Similar phenotypic changes (inhibition of bone growth and tooth eruption) were observed in a study in neonatal rats using a surrogate for denosumab, the RANKL inhibitor osteoprotegerin bound to Fc (OPG-Fc). These changes were partially reversible when dosing of RANKL inhibitor was discontinued. Therefore, treatment with denosumab may impair bone growth in children with open growth plates and may inhibit eruption of dentition.

Preclinical studies in RANK/RANKL-knockout mice suggest absence of RANKL during pregnancy may interfere with maturation of the mammary gland leading to impaired lactation post-partum.

Use in Lactation

It is unknown whether denosumab is excreted in human milk. Knockout mouse studies suggest absence of RANKL during pregnancy may interfere with maturation of the mammary gland leading to impaired lactation post-partum. A decision on whether to abstain from breast-feeding or to abstain from therapy with Xgeva should be made, taking into account the benefit of breast-feeding to the newborn/infant and the benefit of Xgeva therapy to the woman. Encourage women who are breast-feeding during Xgeva treatment to enrol in Amgen's Lactation Surveillance Program. Enrolment may be arranged by telephoning Amgen's Medical Information line on 1800 803 638 (freecall within Australia).

Use in Hepatic Impairment

The safety and efficacy of Xgeva has not been studied in patients with hepatic impairment.

Carcinogenicity

The carcinogenic potential of denosumab has not been evaluated in long-term animal studies. In view of the mechanism of action of denosumab, it is unlikely that the molecule would be capable of inducing tumour development or proliferation.

Genotoxicity

The genotoxic potential of denosumab has not been evaluated. Denosumab is a recombinant protein comprised entirely of naturally occurring amino acids and contains no inorganic or synthetic organic linkers or other non-protein portions. Therefore, it is unlikely that denosumab or any of its derived fragments would react with DNA or other chromosomal material.

Interactions with Other Medicines

No drug-drug interaction studies have been conducted.

In clinical studies, Xgeva has been administered in combination with standard anticancer treatment and in patients previously receiving bisphosphonates. The pharmacokinetics and pharmacodynamics of denosumab were not altered by concomitant chemotherapy and/or hormone therapy nor by previous IV bisphosphonate exposure**.**

Effects on Laboratory Tests

No interactions with laboratory and diagnostic tests have been identified.

Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive or use machinery have been performed.

ADVERSE EFFECTS

Data from three active-controlled multicentre trials were used for the safety analysis in 5677 patients with bone metastases from either prostate cancer, breast cancer, other solid tumours or patients with multiple myeloma (all patients with advanced cancer). A total of 2841 patients were exposed to 120 mg of Xgeva administered once every 4 weeks as a single subcutaneous injection, and 2836 patients were exposed to 4 mg (dose-adjusted for reduced renal function) of zoledronic acid administered once every 4 weeks as an IV infusion. The median (Q1, Q3) duration of exposure to Xgeva for the safety analysis was 12 months (6, 18) for prostate cancer, 17 months (10, 21) for breast cancer, and 7 months (4, 14) for other solid tumours and multiple myeloma.

Table 2 describes adverse events that were reported by ≥ 10% of patients in these studies regardless of presumed causality to study drug.

Table 2: Percentage of Patients with Adverse Events in Patients with Advanced Malignancies Involving Bone by Body System (≥ 10% Incidence in Either Treatment Group)

SYSTEM ORGAN CLASS Preferred Term	Xgeva (N = 2841) n (%)	Zoledronic Acid (N = 2836) n (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anaemia	771 (27.1)	859 (30.3)
GASTROINTESTINAL DISORDERS		
Nausea	876 (30.8)	895 (31.6)
Constipation	603 (21.2)	670 (23.6)
Diarrhoea	577 (20.3)	530 (18.7)
Vomiting	566 (19.9)	570 (20.1)
Abdominal pain	292 (10.3)	280 (9.9)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Fatigue	769 (27.1)	766 (27.0)
Asthenia	607 (21.4)	621 (21.9)
Oedema peripheral	472 (16.6)	462 (16.3)
Pyrexia	409 (14.4)	562 (19.8)
INVESTIGATIONS		
Weight decreased	330 (11.6)	332 (11.7)

METABOLISM AND NUTRITION DISORDERS		
Decreased appetite	656 (23.1)	694 (24.5)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Back pain	718 (25.3)	747 (26.3)
Arthralgia	570 (20.1)	632 (22.3)
Bone pain	564 (19.9)	639 (22.5)
Pain in extremity	524 (18.4)	550 (19.4)
Musculoskeletal pain	357 (12.6)	385 (13.6)
NERVOUS SYSTEM DISORDERS		
Headache	360 (12.7)	382 (13.5)
PSYCHIATRIC DISORDERS		
Insomnia	302 (10.6)	324 (11.4)
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS		
Dyspnoea	585 (20.6)	507 (17.9)
Cough	437 (15.4)	419 (14.8)

N = number of patients who received ≥ 1 active dose of investigational product
n = number of patients reporting ≥ 1 event

Hypocalcaemia

In three phase 3 active-controlled clinical trials in patients with advanced malignancies involving bone, hypocalcaemia was reported in 9.6% of patients treated with Xgeva and 5.0% of patients treated with zoledronic acid. A decrease in serum calcium levels to the range between 1.5 to 1.75 mmol/L was experienced in 2.5% of patients treated with Xgeva and 1.2% of patients treated with zoledronic acid. A decrease in serum calcium levels to < 1.5 mmol/L was experienced in 0.6% of patients treated with Xgeva and 0.2% of patients treated with zoledronic acid.

Osteonecrosis of the Jaw (ONJ)

In three phase 3 active-controlled clinical trials in patients with advanced malignancies involving bone, ONJ was confirmed in 1.8% of patients treated with Xgeva and 1.3% of patients treated with zoledronic acid. Clinical characteristics of these cases were similar between treatment groups. Among subjects with confirmed ONJ, most had a history of tooth extraction, poor oral hygiene, and/or use of a dental appliance. In addition, most subjects were receiving or had received chemotherapy.

Skin Infections (predominantly cellulitis) Leading to Hospitalisation

In three phase 3 active-controlled clinical trials in patients with advanced malignancies involving bone, skin infections leading to hospitalisation (predominantly cellulitis) were reported more frequently in patients receiving Xgeva (0.9%) compared with zoledronic acid (0.7%).

Drug Hypersensitivity Events

In clinical trials in patients with advanced cancer, drug hypersensitivity events were reported in 0.9% and 0.4% of patients treated with Xgeva and zoledronic acid, respectively. A causal relationship to drug exposure has not been established.

Pancreatitis

In a randomised controlled trial in postmenopausal women with osteoporosis receiving 60 mg denosumab or placebo once every 6 months, pancreatitis was reported in 8 patients (0.2%) in the denosumab and 4 patients (0.1%) in the placebo groups. An increased incidence has not been observed in randomised controlled trials in the oncology setting.

DOSAGE AND ADMINISTRATION

Administration should be performed by an individual who has been adequately trained in injection techniques.

The recommended dose of Xgeva is 120 mg administered as a single subcutaneous injection once every 4 weeks into the thigh, abdomen or upper arm. Inject the entire contents of the vial. Do not re-enter the vial.

Supplementation with 500 mg calcium and 400 IU vitamin D is required in all patients, unless hypercalcaemia is present (see PRECAUTIONS, Vitamin Supplementation and Hypocalcaemia).

No dose adjustment is necessary in elderly patients (see PRECAUTIONS, Use in the Elderly) or in patients with renal impairment (See PRECAUTIONS, Renal Impairment).

Xgeva is a sterile and preservative-free product. Before administration, the Xgeva solution should be inspected for particulate matter and discolouration. Do not use if the solution is cloudy or discoloured. Do not shake excessively. To avoid discomfort at the site of injection, allow the vial to reach room temperature (up to 25°C) before injecting, and inject slowly. A 27 gauge needle is recommended for the administration of Xgeva.

Product is for single-use in one patient only. Dispose of any medicinal product remaining in the vial.

OVERDOSAGE

There is no experience with overdosage with Xgeva. Xgeva has been administered in clinical studies using doses up to 180 mg every 4 weeks (cumulative doses up to 1080 mg over 6 months), and 120 mg weekly for 3 weeks.

PRESENTATION AND STORAGE CONDITIONS

Xgeva is supplied as a sterile, preservative-free, clear, colourless to slightly yellow solution for injection at pH 5.2. The solution should not be used if cloudy or discoloured. The solution may contain trace amounts of translucent to white proteinaceous particles.

Each vial contains a deliverable dose of 120 mg denosumab in 1.7 mL of solution (70 mg/mL). Product is for single use in one patient only. Dispose of any medicinal product remaining in the vial.

It is recommended to store vials in a refrigerator at 2°C to 8°C in the original carton. Do not freeze. Protect from direct light. Do not excessively shake the vial. Do not expose to temperatures above 25°C.

If removed from the refrigerator, Xgeva should be kept at room temperature (up to 25°C) in the original container and must be used within 30 days.

Pack size of one or *four.

* Not marketed in Australia.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4 Prescription Medicine

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29 August 2011

Therapeutic Goods Administration

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