Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Denosumab

Proprietary Product Name: Prolia

Sponsor: Amgen Australia Pty Ltd

January 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

Product Details

Type of Submission	New Biological Entity
Decision:	Treatment of osteoporosis in postmenopausal women - approved Treatment of bone loss associated with hormone ablation in men with prostate cancer - rejected
Date of Initial Decision:	2 June 2010
Date of Final Decision:	26 October 2010
Active ingredient(s):	Denosumab
Product Name(s):	Prolia
Sponsor's Name and Address:	Amgen Australia Pty Ltd Level 7, 123 Epping Road North Ryde, NSW 2113
Dose form(s):	Solution for injection
Strength(s):	60 mg/mL
Container(s):	Pre-filled syringe 1 mL, glass barrel (1 mL) with staked-in-place needle (type 304 stainless steel) Pre-filled syringe 1 mL with automatic needle guard Glass vial 1 mL, elastomeric stopper and aluminium seal
Pack size(s):	1
Approved Therapeutic use:	The treatment of osteoporosis in postmenopausal women. Prolia significantly reduces the risk of vertebral, non-vertebral and hip fractures
Route(s) of administration:	Subcutaneous injection
Dosage:	Once every 6 months
ARTG Numbers:	159322, 159323, 159324

Product Background

Denosumab is a new chemical entity. It is a fully human monoclonal antibody of the IgG_2 subclass, possessing a high specificity and affinity for human receptor activator of nuclear factor kappa B (RANK) ligand.

Osteoporosis is a systemic disease of the skeleton characterized by low bone mass and deterioration of normal bony micro-architecture causing increased bone fragility and susceptibility to fracture.[1] It is by far the most common metabolic bone disease worldwide and is the leading cause of fractures in the elderly. Women aged over 50 are said to have a 40% lifetime fracture risk as a result of osteoporosis with common fracture sites being the

[1] Nalamachu, SR and Nalamasu, S. Osteoporosis (Primary). *eMedicine.com*. [Online] 25 September 2008. [Cited: 15 August 2009.] http://emedicine.medscape.com/article/311331-overview.

vertebrae, wrist and hip. In the US, approximately half of all patients who have had a hip fracture never recover fully. The excess mortality rate of a hip fracture is estimated to be 20% within 12 months.[2]

According to Osteoporosis Australia, someone is admitted to an Australian hospital with an osteoporotic fracture every five minutes.[3] Extrapolating data on Australia's aging population this is expected to increase to one every three minutes by the year 2021. Half of all women aged over 60 will have an osteoporotic fracture at some point. These instances suggest a considerable morbidity burden on health care in Australia.

The pathogenesis of osteoporosis is complex but understood to involve an imbalance between the rate of bone resorption and bone formation, both of which occur constantly in the form of matrix remodelling in healthy bone.[4] New bone is deposited by marrow-derived cells called osteoblasts, whereas bone resorption is facilitated by stimulation of cells called osteoclasts. As it is currently understood, there are three mechanisms whereby osteoporosis develops: an inadequate peak bone mass (established during growth), excessive bone resorption (strongly influenced by hormonal factors) and inadequate formation of new bone during remodelling. The rate of osteoclast activity (and hence bone resorption) is sensitive to oestrogen and the precipitous fall in circulating oestrogen following menopause is understood to be the major mechanism for post-menopausal osteoporosis.[5,6]

Diagnosis of osteoporosis is conventionally made by estimates of bone mineral density. The most common method involves dual energy x-ray absorptiometry (DEXA) scanning. This technique is regarded as the "gold standard" against which other techniques of bone mineral density are compared.[7] DEXA scanning is most commonly applied to the lumbar vertebrae and femoral neck as these being sites are most vulnerable to fracture. The technique produces an areal (two-dimensional) density used as a surrogate for volumetric (three-dimensional) density. A simple statistical transformation compares this density to that of the mean of a healthy young adult population (the so-called "T-score") or to age-matched controls (the "Z-score").[8] The World Health Organization considers a T-score of minus 2.5 or below (more than 2½ standard deviations from the mean of a young healthy population) as diagnostic for osteoporosis.[9] A T-score between -1.0 and minus 2.5 is labelled osteopenia, and a T-score of greater than -1.0 is considered normal.

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[2] Cummings ST et al. Risk factors for hip fracture in white women. N Engl J Med 1995; 332: 767-773.

[3] Osteoporosis Australia. What is Osteoporosis? *Osteoporosis Australia*. [Online] Osteoporosis Australia, 15 August 2009. [Cited: 15 August 2009.] http://www.osteoporosis.org.au/osteo_osteoporosis.php.

[4] Raisz L. Pathogenesis of osteoporosis: concepts, conflicts, and prospects. J Clin Investigation 2005; 115: 3318-3325.

[5] Kanis JA**.** *Osteoporosis*. Oxford : Blackwell Science, 1997.

[6] Riggs BL, Khosla S and Melton, LJ. A unitary model for involutional osteoporosis: estrogen deficiency causes both type I and type II osteoporosis in postmenopausal woman and contributes to bone loss in aging men. J Bone Mineral Research 1998; 13: 763-773.

[7] WHO Scientific Group on the Prevention and Management of Osteoporosis. Prevention and Management of Osteoporosis. World Health Organization. Geneva : s.n., 2003.

[8] Gilsanz V. Bone Density in Children: a review of the available techniques and indications. Eur J Radiol 1998; 26:177-182.

[9] World Health Organization Study Group. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Geneva : World Health Organization, 1994.

Conventional therapy for osteoporosis and bone loss has been multifaceted. Modification of lifestyle factors, such as weight-bearing exercise[10] and nutrition[11], supplementation of diet with, in particular, calcium[12] and vitamin D[13] and, where appropriate, hormonal manipulation have also been used. While the overall use of and indications for oestrogen replacement therapy remain controversial this treatment does result in (statistically significantly) fewer fractures in postmenopausal women.[14] Some selective oestrogen receptor modulators (such as raloxifene) have also proven effective in this regard.[15]

The bisphosphonate group of drugs forms the main pharmacological treatment for osteoporosis and are considered by many to be first-line treatment for women with proven disease.[16] Commonly prescribed agents in this class in Australia include alendronate, risedronate and zoledronate. Many have been in use since the 1960s when they were believed to act by preventing the dissolution of the important bone mineral hydroxyapatite. They are now believed to act by a different mechanism (inhibition of farnesyl diphosphate synthase) resulting in a decrease in osteoclast functional activity). Although efficacious, these pharmaceuticals feature a number of adverse effects which can limit their use, particularly upper gastrointestinal tract irritation. More recently, osteonecrosis of the jaw[17] and long-term over-suppression of subtrochanteric bone turnover have been raised as concerns.[18] Other novel therapies under investigation include recombinant parathyroid hormone and strontium but these agent have known and potentially limiting adverse effects.[19,20]

A range of molecular signals have been implicated in the activation of osteoclasts. One of the best studied is Receptor Activator of Nuclear factor Kappa B (RANK). RANK is a transmembrane protein expressed on the surface of osteoclasts. Upon binding of the RANK ligand - a member of the tumour necrosis factor family of signalling molecules - osteoclast activity is stimulated and bone resorption increases.[21] It has been recognized for a number of

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[10] Bonaiuti, D et al. Exercise for prevnting and treating osteoporosis in postmenopausal women. The Cochrane Library. [Online] March 2009. [Cited: 15 August 2009.] http://mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD000333/frame.html.

[11] Joint WHO/FAO/UNU Expert Consultation. Protein and amino acid requirements in human nutrition. Geneva : World Health Organization, 2007. pp. 224-226.

[12] Tang BM, et al. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. Lancet 2007; 370: 657-666.

[13] Bischoff-Ferrari HA, et al. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. JAMA 2005; 293: 2257-2264.

[14] Roussouw JE, Anderson GL and Prentice RL. Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women. JAMA 2002; 288: 321-333.

[15] Meunier PJ, et al. Treatment of postmenopausal women with osteoporosis or low bone density with raloxifene. Osteoporosis International 1999; 10: 330-336.

[16] Lyles KW, Colon-Emeric CS and Magaziner JS. Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med 2007; 357: 1799-1809.

[17] Woo S, Hellstein J and Kalmar J. Narrative review: bisphosphonates and osteonecrosis of the jaws. Ann Intern Med 2006; 144: 753-761.

[18] Lenart BA, Lorich DG, Lane JM. Atypical fractures of the femoral diaphysis in postmenopausal women taking alendronate. N Engl J Med 2008; 358: 1304.

[19] Honeywell M, Phillips S and Branch E. Teriparatide for osteoporosis: a clinical review. Pharm Ther J 2003; 28: 713-716.

[20] Meunier PJ, Roux C, Seeman E. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. N Engl J Med 2004; 350: 459-468.

[21] McHugh K. Osteoimmunology in skeletal cell biology and disease. Autoimmunity 2008; 41:181-182.

years that modulation of these systems could provide an opportunity for novel therapeutics in the treatment of osteoporosis.[22]

Denosumab is a human monoclonal antibody of the immunoglobulin G_2 (IgG_2) subclass directed against RANK ligand. It is produced in genetically engineered Chinese hamster ovary cells. It binds with a high degree of specificity and affinity to RANK ligand preventing the activation of RANK and thus the stimulation (and reduction in number) of osteoclasts. The pharmaceutical's antiresorptive activity results in increased cortical and trabecular bone mass, volume and strength.[23]

The proposed indication for denosumab includes the treatment of postmenopausal osteoporosis (PMO) and the treatment of bone loss associated with hormone ablation in men with prostate cancer and in women with breast cancer. Hypocalcaemia is listed as a contraindication to the product.

The proposed dosage is 60 mg administered subcutaneously every six months. No adjustment to the dosage is proposed for the elderly or in the setting of renal failure.

Regulatory Status

On 26 May 2010, the European Commission approved the use of denosumab for: *treatment of osteoporosis in postmenopausal women at increased risk of fractures. Prolia significantly reduces the risk of vertebral, non vertebral and hip fractures. Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. In men with prostate cancer receiving hormone ablation, Prolia significantly reduces the risk of vertebral fractures.*

On 1 June 2010, the US FDA granted approval of Prolia for *the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factures for fracture: or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Prolia reduces the incidence of vertebral, non-vertebral and hip fractures.*

An additional therapeutic indication was sought in the US, namely for the use of this pharmaceutical for the prevention of PMO. It is further understood that an FDA panel met on 13 August 2009 and voted unanimously to support denosumab's use for the treatment of PMO and bone loss associated with hormone ablation in prostate cancer but did not support its use for the treatment of bone loss associated with hormone ablation in breast cancer and prevention of PMO.[24] Details of the FDA's decision have not yet been published but media reports state that the panel did not support the use of denosumab to prevent PMO, indicating that its risk profile did not justify its registration as a prophylactic therapy.[25] The FDA also issued a Complete Response letter for the hormone ablation bone loss trial (HALT) indications (non-metastatic prostate cancer and non-metastatic breast cancer) and the PMO prevention indication. The FDA Complete Response letter relating to the HALT indications

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[22] Theill LE, Boyle WJ, Penninger JM.. RANK-L and RANK: T Cells, Bone Loss, and Mammalian Evolution. Ann Rev Immunol 2002; 20: 795-823.

[23] Kostenuik PJ. Osteoprotegrin and RANKL regulate bone resorption, density, geometry and strength. Curr Opin Pharmacol 2005; 5: 618-625.

[24] Dooren JC. The Wall Street Journal. *The Wall Street Journal.* [Online] The Wall Street Journal, 13 August 2009. [Cited: 15 August 2009.] http://online.wsj.com/article/BT-CO-20090813-714388.html.

[25] Walker, EP. FDA Panel Backs Denosumab for Osteoporosis, But Not Osteopenia. *Medpage Today.* [Online] 13 August 2009. [Cited: 11 September 2009.] http://www.medpagetoday.com/Endocrinology/Osteoporosis/15530.

requested additional information on cancer outcomes in patients with underlying breast or prostate cancer. Amgen plans to submit a response to the FDA Complete Response letter addressing this request.

Applications to market the product have been submitted to regulatory authorities in the Canada (December 2008) and Switzerland (February 2009).

Product Information

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

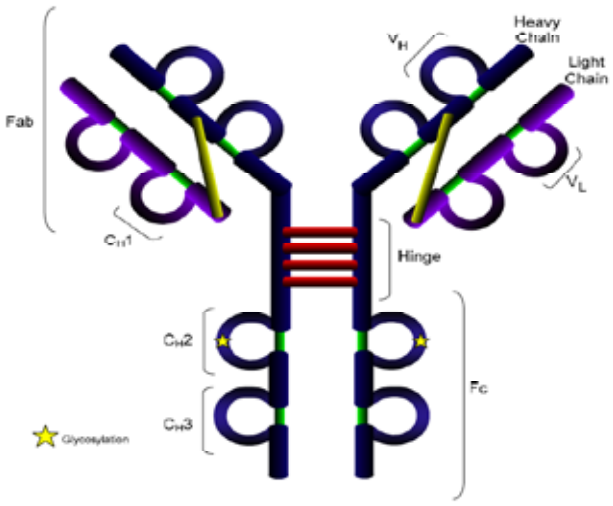
II. Quality Findings

Drug Substance (active ingredient)

Structure

Denosumab is a full-length human monoclonal antibody of the IgG2 subclass consisting of 2 heavy chains and 2 light chains of the kappa subclass (Figure 1). Denosumab contains 36 total 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 2 intramolecular disulfides. Each heavy chain contains 448 amino acids with 4 intramolecular disulfides. The terminal lysine 488 is typically removed during cell culture.

Figure 1. Schematic of Denosumab Structure



Manufacture

Denosumab is manufactured by a cell culture bioreactor process of transfected Chinese Hamster Ovary (CHO) cells that produce recombinant denosumab. The medium around the CHO cells is purified to produce a single batch of pharmaceutical substance. The purification process consists of 3 chromatography steps (including protein A, cation exchange and hydrophobic interaction chromatography) and viral inactivation steps.

The Cell banking processes were assessed to be satisfactory.

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

Physical and Chemical Properties

Physical and chemical properties are shown in Table 1.

Table 1. Physical and Chemical Properties of Denosumab

Expression System	CHO cells and encoded by cDNAs
Immunoglobulin subclass	IgG2
Sequence	Fully Human Sequence
Binding site	Specific Binding to human RANKL at the D-E Loop (epitope:DLATE)
Molecular weight	144,462 Da for deglycosylated molecule[a]
	147,352 Da including glycosylation[b]
Cysteines	36
Number of disulfide bonds	18
Glycosylation	N-linked site: Asn-298 of each heavy chain
Theoretical extinction coefficient	1.4 mL/(mg*cm) at 280 nm
Isoelectric point	8.3 to 8.5, determined experimentally by cIEF
T_m (melting points)	Approximately 69°C to 72°C for C_H2, 76°C for Fab, and 83°C for C_H3 domains, respectively

[a] For peptide portion; accounting for C-terminal Lysine processing at the heavy chain
[b] Glycosylated mass includes 2 copies of the most abundant G0 glycan

Specifications

The proposed specifications, which control identity, content, potency, purity and other biological and physical properties of the pharmaceutical substance relevant to the dose form and its intended clinical use, have been reviewed and are satisfactory.

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

Stability

Stability data have been generated under real time/stressed conditions to characterise the stability/degradation profile of the pharmaceutical substance and to establish a shelf life of 36 months at minus 30°C.

Drug Product

Formulation(s)

Denosumab 60 mg/mL is registered as either;

- a pre-filled syringe (PFS)
- a pre-filled syringe with automatic needle guard (PFS-ANG)
- a vial

Denosumab is intended as a single use, preservative free solution for subcutaneous injection. The pharmaceutical product is manufactured by diluting drug substance (70 mg/mL) to a target concentration of 60 mg/mL using a formulation buffer containing 10 mM acetate and 5% (w/v) sorbitol at a pH of 5.2. Polysorbate 20 is also added during preparation to the PFS preparations. The resulting pharmaceutical product contains

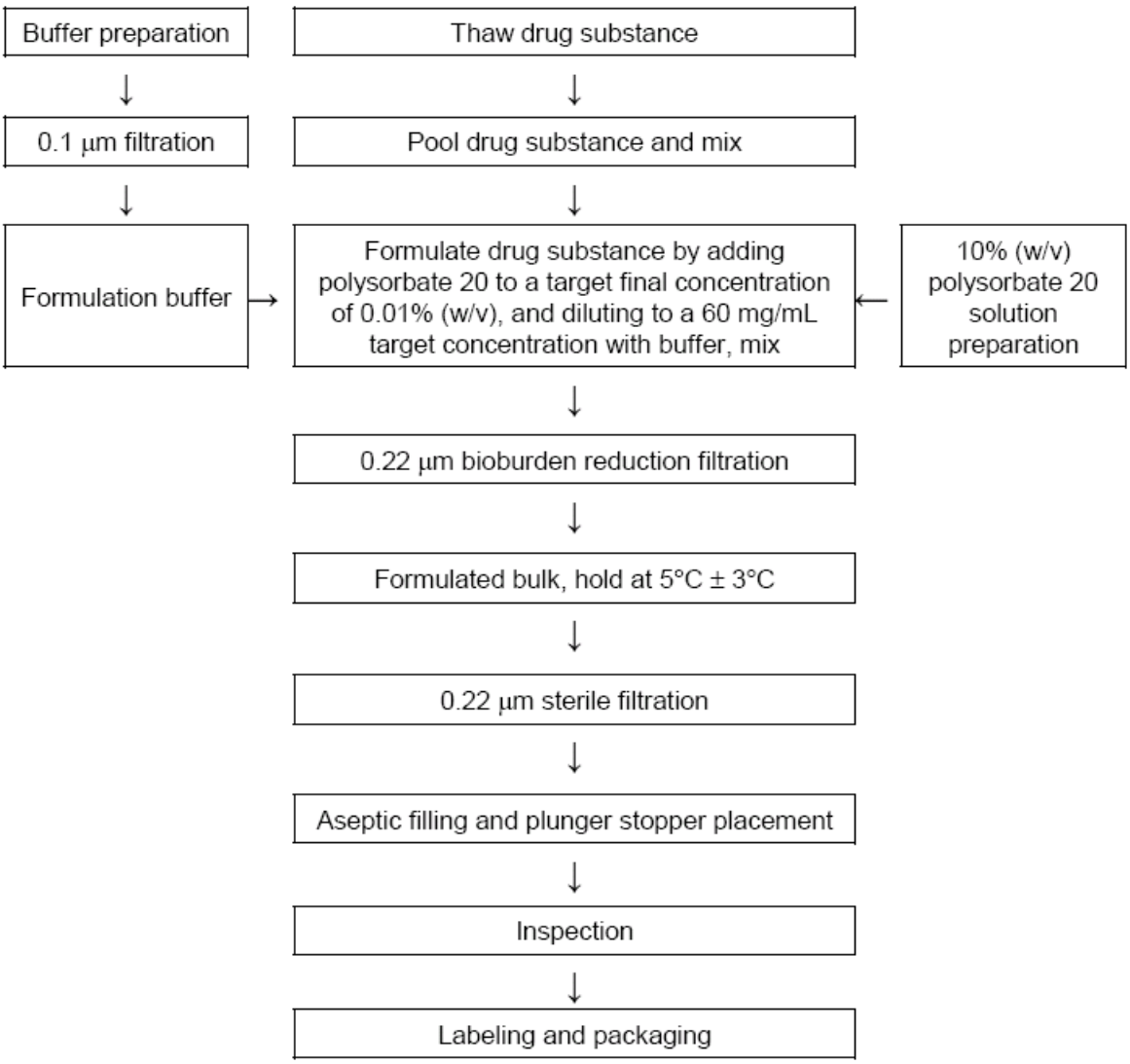
- 60 mg/mL denosumab
- 17 mM acetate (1 mg/mL)
- 4.7% (47 mg/mL) sorbitol
- 0.01% (0.01 mg/mL) polysorbate 20 (PFS and PFS-ANG only)

The PFS comprises a type 1 glass barrel (1 mL) with a staked-in-place (integrated) needle (type 304 stainless steel). The plunger stopper is made of bromobutyl rubber (West formula 4023/50 grey or equivalent) and is laminated with a fluoropolymer film on the product contact surface. The elastomeric needle shield is made from natural rubber (West formula 7974/50 grey or equivalent) and may be supplemented with an outer polypropylene rigid needle shield. The glass barrel, plunger stopper and needle shield comply with European Pharmacopoeia (Ph Eur) requirements. The PFS product may also be supplied with an automatic needle guard (ANG). The ANG body is made of polycarbonate and includes a stainless steel spring. The plunger rod is made of polypropylene. The ANG is considered a functional secondary packaging component of the finished pharmaceutical product. The vial consists of a 3 cubic cm Type 1 glass vial, elastomeric stopper and aluminium seal with flip-off cap. All comply with Ph Eur requirements.

Manufacture for PFS and PFS-ANG product

The manufacturing process is outlined at Figure 2.

Figure 2: Overall Drug Product Manufacturing Process Flow Chart



Specifications

The proposed specifications for the pre-filled syringe and vial presentations, which control identity, potency, purity, dose delivery and other physical, chemical and microbiological properties relevant to the clinical use of the product have been reviewed and are considered satisfactory.

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

Stability

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. The proposed shelf life is 30 months when stored between 2 to 8°C. Denosumab is degraded by light but is quite resistant to degradation by elevated temperatures.

Stability studies support a shelf life of 30 months at 2 to 8 °C for all presentations.

Biopharmaceutics

Biopharmaceutical data has not been evaluated as biopharmaceutic data are not normally required for monoclonal antibodies.

Quality Summary and Conclusions

The administrative, product usage, chemical and pharmaceutical 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.

All outstanding issues regarding evaluation of quality data and recommendations of the Pharmaceutical Subcommittee (PSC) of the Australian Drug Evaluation Committee (ADEC) have been addressed in a satisfactory manner. There are no outstanding issues regarding endotoxin content, container safety, sterility or viral safety or Good Manufacturing Practice (GMP) clearance.

As with all new biological entities, batch release testing of the first five batches by the TGA's Office of Laboratories and Scientific Servicers (OLSS) is recommended to verify quality and consistency of manufacture. Subject to the Delegate's agreement, batch release conditions should be added to the conditions of registration of this product.

III. Nonclinical Findings

Introduction

The general quality of the nonclinical studies was high. The safety-related studies were all conducted under Good Laboratory Practice (GLP) conditions and used the clinical route of administration (subcutaneous [SC]). The primary pharmacology studies examined *in vitro* and *in vivo* efficacy; the discussion on the mechanism of action was mainly drawn from published literature. No specific secondary pharmacodynamic studies were submitted although specificity and tissue cross-reactivity were explored in other studies. Safety pharmacology studies examined cardiovascular effects in monkeys and effects on bone and tooth development in neonatal rats. The toxicology studies examined repeat-dose toxicity as well as reproductive toxicity. The overall data package was consistent with the TGA-adopted EU guideline.[26] Toxicology studies were conducted with denosumab manufactured using an early version of the intended commercial process. A comparative pharmacokinetic/pharmacodynamic study was conducted in cynomolgus monkeys with batches of denosumab prepared by this manufacturing process (CP1), and the one developed for commercial use (CP2), revealing no differences in the drug's biological activity or kinetics.

Pharmacology

Primary pharmacology

Rationale and mechanism of action

The receptor activator of nuclear factor kappa-B (RANK) ligand (RANKL) is a key mediator in the pathway required for the formation, function and survival of osteoclasts, the cells involved in bone resorption. RANKL binds to RANK on osteoclast precursors and also on mature osteoclasts. It promotes differentiation of the precursor cells into osteoclasts and stimulates mature osteoclasts to resorb bone. Inhibition of RANKL is a biologically plausible intervention point in diseases associated with increased bone resorption. Denosumab is a

[26] EMEA, Committee for Proprietary Medicinal Products (CPMP), 16 July 1997. Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals, CPMP/ICH/302/95.

human IgG2 antibody that binds to RANKL thereby neutralising the ligand and suppressing osteoclast-mediated bone turnover.

In vitro studies

Denosumab was shown to bind to human RANKL with high affinity (K_D, ~3 pM). The antibody did not recognise murine RANKL nor bind to other members of the human tumour necrosis factor (TNF) family. In cell culture, denosumab inhibited the formation of osteoclasts that relied on human RANKL but not in cultures that relied on murine RANKL.

In vivo studies

Denosumab (25 or 50 mg/kg SC, once monthly) decreased bone resorption, increased bone mass and bone mineral density and improved bone strength in a 16-month study in cynomolgus monkeys which had been subject to ovariectomy. Efficacy was also evident in the repeat-dose toxicity studies conducted in young adult male and female monkeys, with dose-dependent reductions in bone resorption markers seen at all doses tested (≥0.1 mg/kg SC, once weekly), increased bone mineral density observed in males treated at ≥1 mg/kg SC once weekly in the 1-month study and increased bone mineral density, bone mineral content, bone mass and mechanical strength observed at doses of 10 or 50 mg/kg SC once monthly in the 6/12-month study.

Reflecting the species specificity of the antibody, denosumab did not display efficacy in either mice or rats. The drug did inhibit hypercalcaemia in mice challenged with human RANKL. A surrogate of denosumab, recombinant human osteoprotegerin bound to Fc (huOPG-Fc), able to recognise rodent RANKL, was therefore used in a number of studies in rodents. OPG is an endogenous soluble decoy receptor for RANKL; thus, it has a comparable mechanism of action to denosumab. An increase in bone mass following treatment with huOPG-Fc was demonstrated in rats. Other *in vivo* studies were carried out in mice genetically modified to carry a chimeric human/mouse RANKL gene. This form of RANKL was recognised by denosumab. Treatment with either huOPG-Fc or denosumab (5 mg/kg SC, twice weekly) caused similar reductions in bone resorption. In a study on femoral fracture healing in these mice, the calluses in denosumab-treated animals had greater bone mineral content, bone area and bone volume compared with untreated controls.

Transition from 6 months of treatment with the bisphosphonate, alendronate (50 µg/kg intravenous [IV] bi-weekly), to denosumab (25 mg/kg SC, once monthly) in adult monkeys which had been subject to ovarian ablation did not lead to any adverse effects on serum calcium or bone strength but led to additional reductions in bone resorption/increases in bone mineral density compared to continuous treatment with alendronate.

Secondary pharmacodynamics and safety pharmacology

Specific studies to evaluate the potential secondary pharmacodynamic effects of denosumab have not been conducted. The sponsor has argued that the secondary pharmacodynamic endpoints in the general toxicity studies together with the extensive literature available on denosumab and RANK/RANKL are sufficient to address these issues. The main focus of these published studies has been on the immune system as RANK and RANKL are expressed on cells of the immune system in addition to cells involved in bone remodelling (Hsu *et al.*, 1999; Lacey *et al.*, 1998; Leibbrandt and Penninger, 2008).[27,28,29,30] The literature identifies

[27] Hsu H, Lacey DL, Dunstan CR, *et al.* Tumor necrosis factor receptor family member RANK mediates osteoclast differentiation and activation induced by osteoprotegerin ligand. *Proc Natl Acad Sci USA*. 1999; 96: 3540–3545.

some specific situations where RANKL inhibition in rodents may affect the immune system, including the developmental absence of lymph nodes in RANK/RANKL knock-out mice (Kong *et al.*, 1999b; Dougall *et al.*, 1999; Mebius, 2003).[31,32,33] However, inhibition of RANK/RANKL in mice or rats over-expressing OPG did not result in defects in lymph node formation (Simonet *et al.*, 1997; Stolina *et al.*, 2005, 2006, 2007).[34,35,36,37,38,39] The development of lymph nodes was not examined in the submitted embryofetal development study in cynomolgus monkeys; however, no adverse effects on the functioning of the immune system (based on examination of immunoglobulin levels, immunophenotyping of lymphocytes, the T-cell dependent antibody response and/or the histopathology of lymphoid tissues) were noted in the species in the repeat-dose toxicity studies at exposures ≤150 times the clinical exposure or in the 16-month pharmacology study at exposures ≤95 times the clinical exposure (based on the area under the plasma concentration time curve [AUC] and accounting for the increased dosing frequency).

Specific safety pharmacology studies were conducted to examine the potential for cardiovascular and respiratory effects in monkeys as well as the potential for effects on bone growth and tooth eruption in neonatal rats. A single SC dose of denosumab up to 30 mg/kg caused no treatment-related effects on electrocardiogram (ECG) parameters, blood pressure, heart rate or respiration (measured at around the time to maximal plasma concentration (T_{max}); 72 hours); this dose produced peak levels of denosumab ~40-times higher than that expected in patients. No ECG abnormalities were observed in the 12-month repeat-dose toxicity study in monkeys at doses up to 50 mg/kg SC (although readings were taken at 2–4 hours post-dose, much sooner than the T_{max}). There was no *in vitro* examination of the

[28] Lacey DL, Timms E, Tan HL, *et al*. Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. *Cell.* 1998; 93: 165–176.

[29] Leibbrandt A, Penninger JM. RANK/RANKL: regulators of immune responses and bone physiology. *Ann NY Acad Sci.* 2008; 1143: 123–150.

[30] Penninger CL, Patel NM, Niebur GL, Tovarb A, Renaud JE. A fully anisotropic hierarchical hybrid cellular automaton algorithm to simulate bone remodeling Mech Res Comm 2008; 35: 32-42.

[31] Kong Y-Y, Yoshida H, Sarosi I, *et al*. OPGL is a key regulator of osteoclastogenesis, lymphocyte development and lymph node organogenesis. *Nature.* 1999b; 397: 315–323.

[32] Dougall WC, Glaccum M, Charier K *et al.* RANK is essential for osteoclast and lymph node development. *Gene and Dev*. 1999; 13: 2412–2423.

[33] Mebius, RE. Organogenesis of lymphoid tissues. *Nat Rev Immunol.* 2003; 3: 292–303.

[34] Simonet WS, Lacey DL, Dunstan CR, *et al*. Osteoprotegerin: a novel secreted protein involved in the regulation of bone density. *Cell.* 1997; 89: 309–319.

[35] Stolina M, Adamu S, Dwyer D, *et al*. RANKL inhibition with osteoprotegerin (OPG) prevents bone loss but does not affect immune status in arthritic rats. *J Bone Min Res.* 2005a: 20 (suppl 1): S257.

[36] Stolina M, Dwyer D, Morony S, *et al.* Rats and mice overexpressing soluble OPG have high bone mass but no alteration in immunological parameters or lymphocyte function. *Arthritis Rheumat.* 2005b; 20(suppl N9): S708.

[37] Stolina M, Dwyer D, Grisanti M, Kostenuik PJ, Zack DJ. Continuous RANK ligand inhibition in OPG transgenic mice is not associated with changes in innate or humoral immune responses. EULAR; June 21–24, 2006a; Amsterdam, Holland.

[38] Stolina M, Dwyer D, Ominsky MS, *et al.* Rats overexpressing soluble OPG from a prenatal stage exhibit high bone mass phenotype but no alteration in the development of lymphoid organs or in innate immune response. *Aegean Conferences Series.* 2006b; 22: 125–126.

[39] Stolina M, Dwyer D, Ominsky MS, *et al.* Continuous RANKL inhibition in osteoprotegerin transgenic mice and rats suppresses bone resorption without impairing lymphorganogenesis or functional immune responses. *J Immunol*. 2007; 179: 7497–7505.

potential for inhibition of the human ether-à-go-go related gene (hERG) K^+ channel current; the sponsor justified this on the basis of the large size of denosumab (150 kDa), which restricts intracellular penetration and access to the channel. This is acceptable, considering also the lack of effects on the ECG of monkeys *in vivo*.

The literature reports that RANK/RANKL knock-out mice have a failure of tooth eruption (Kong et al, 1999; Fata et al. 2000),[40,41] which is consistent with the requirement for bone resorption in normal tooth eruption (Marks *et al.*, 1995; Marks and Schroeder, 1996).[42,43] The RANKL inhibitor, rat osteoprotegerin fragment (OPG-Fc), as well as the bisphosphonate, alendronate, both reduced bone growth (as well as body weight) and inhibited tooth eruption in 2-week old neonatal rats at 10 mg/kg SC per week for 6 weeks.

Pharmacokinetics

Nonclinical pharmacokinetic studies were conducted in mice, rats and cynomolgus monkeys to support the pharmacology and toxicity studies conducted in mice and monkeys. A comparative pharmacokinetic study was also conducted on denosumab prepared by the two separate manufacturing processes.

Absorption of denosumab into the systemic circulation after SC administration was slow in all species, with peak serum concentrations achieved at 72 hours post-dose in mice, rats and monkeys, and at 1–4 weeks in humans.

In mice and rats, species in which denosumab does not bind to RANKL, the IV pharmacokinetics of denosumab were linear over the dose range 0.1 to 10 mg/kg. Serum half-life was very long, approximately 19 days in mice and 11 days in rats. Bioavailability after SC administration was moderate to high (86% in mice and 56% in rats). In huRANKL knock-in mice, the exposure and half-life were both significantly reduced (by ~5–6-times) 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 antibodies (for example, the maximal plasma concentration [C_{max}] and 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 the recommended clinical dose (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 ^{125}I-denosumab in the monkey. Although tissue distribution of radioactivity was wide, peak concentrations in tissues were all below that for

[40] Kong Y-Y, Feige U, Sarosi I, *et al.* Activated T cells regulate bone loss and joint destruction in adjuvant arthritis through osteoprotegerin ligand. *Nature.* 1999a; 402: 304–309.

[41] Fata JE, Kong YY, Li J, *et al.* The osteoclast differentiation factor osteoprotegerin-ligand is essential for mammary gland development. *Cell.* 2000; 103: 41–50.

[42] Marks, SC, Gorski JP, Wise GE. The mechanisms and mediators of tooth eruption – Models for developmental biologists. Int J Dev Biol. 1995; 39: 223–230.

[43] Marks SC, Schroeder HE. Tooth eruption: Theories and facts. *Anat Rec.* 1996; 245: 374–393.

serum, except for at the injection site and the thyroid. 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 TCA-precipitable and therefore likely to represent intact antibody. No conventional metabolism studies were submitted; this is acceptable for a protein pharmaceutical 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.

Relative exposure

Exposure ratios have been calculated based on animal:human AUC values adjusted for dosing frequency (Tables 2,3). Calculations are made with reference to a human value of 448 µg·day/mL for the mean area under the plasma concentration time curve for a dosing interval ($AUC_{0-\tau}$) over the 6-month dosing interval obtained after the second 60 mg SC dose (the recommended clinical dose) in Study 20010223; the C_{max} at this dose was 6.94 µg/mL. A significant exposure margin is demonstrated between the upper dose levels used in the toxicity studies compared with the proposed clinical dose.

Table 2: Relative exposure in repeat-dose toxicity 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	0.8
					1	3.41	8
					10	42.0	102
				IV	**10**	68.6	166
102090		6/12 months	Once monthly	SC	10	48.2	27
					50	268	150

ÿ [1] *NOAEL (No Observable Adverse Effect Level) shown in bold text.*
[2] *Based on a human $AUC_{0-\tau}$ of 10.752 mg·h/mL (= 448 µg·day/mL), obtained at the recommended clinical dose (60 mg) in Study 20010223; animal:human AUC values are compared following multiplication of the animal AUC values by 26 (for once-weekly administration) or 6 (once-monthly administration) to account for the higher dosing frequency employed in the animal studies compared with the 6-monthly administration in humans.*

Table 3: 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	10
				5	16.4	40
				12.5	67.8	164
102842 *Embryofetal development*		Once weekly (over GD20–50)	SC	2.5	8.80	21
				5	15.5	37
				12.5	41.0	99

ÿ [1,2] *As in the preceding table;*
AUC data for the embryofetal development study are for animals negative for neutralising antibodies.

Toxicology

Species selection

As denosumab is not pharmacologically active in rodents, cynomolgus monkeys were selected for the evaluation of repeat-dose and reproductive toxicity.

Single-dose toxicity

No single-dose toxicity studies were performed. This is acceptable in light of the data obtained in the cardiovascular/respiratory safety study and the repeat-dose toxicity studies in cynomolgus monkeys.

Repeat-dose 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. The studies were appropriately designed and conducted. In both studies, there was little evidence of toxicity. Changes that were noted were related to the pharmacological effects of denosumab. Mortality was observed in 2/8 animals in the 50 mg/kg dose group in the 12-month study but this is considered to be due to infection (with *Giardia* and/or *Cryptosporidium*) rather than related to treatment. 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. Increased thyroid weight was observed at 10 mg/kg/week IV in the first study but not at 50 mg/kg/month SC in the second study (producing comparable exposure); this was reversible and not accompanied by histopathological changes. Gross and microscopic pathological examinations did not reveal any treatment-related effects except in the bone tissue (that is, 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 C_{max} and AUC) increased in a dose-related manner. The 12-month study establishes a No Observable Adverse Effect Level (NOAEL) of 50 mg/kg SC for once monthly administration, a dose yielding 150-times the clinical exposure to denosumab at the recommended dose (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 TGA-adopted guideline.[26] Furthermore, rodent carcinogenicity studies would be inappropriate due to the animals' lack of pharmacodynamic responsiveness to denosumab.

Reproductive toxicity

Reproductive toxicity studies comprised a fertility study and an embryofetal development study in the cynomolgus monkey. A pre-/postnatal development study was not conducted; its absence was justified by the sponsor on the grounds that the need to conduct the study in non-human primates due to the species specificity of denosumab would significantly limit the

number of neonates available for evaluation and therefore the value of the study. This is considered acceptable, given the absence of adverse effects identified in the embryofetal developmental study. However, the literature reports of an absence of lactation in RANK/RANKL knock-out mice through inhibition of mammary gland maturation (Fata *et al.*, 2000) and the potential for denosumab to have this effect could not be assessed in the embryofetal development study.[41] Appropriate cautionary statements in the PI are therefore warranted.

Placental transfer of denosumab was demonstrated in the cynomolgus monkey. No nonclinical data on the excretion of denosumab in milk were submitted. As an immunoglobulin G (IgG), some excretion of denosumab in milk is expected but oral absorption in the nursing infant is unlikely.

Female fertility and menstrual cycles were unaffected by treatment with denosumab at doses up to 12.5 mg/kg/week SC (relative exposure based on AUC, 164); progesterone, oestradiol and luteinizing hormone levels were also unaffected by treatment. No male fertility study was conducted but assessment of sperm motility and histopathological examination of male reproductive tissues in the 12-month repeat-dose toxicity study in cynomolgus monkeys revealed no adverse effects for denosumab (≤50 mg/kg/month SC; relative exposure, 150).

Administration of denosumab (≤1 2.5 mg/kg SC) once weekly during the period of organogenesis in cynomolgus monkeys did not affect fetal weight and there was no evidence of a treatment-related increase in fetal variations or malformations. Exposure at the highest dose was approximately 100 times higher than the clinical exposure (based on AUC). While the small number of fetuses available in the monkey embryofetal toxicity study limits its power to reveal potential adverse effects, the high exposure multiple that was achieved goes some way to compensate for this. However, as noted earlier, lymph node development was not examined in this study and this was a concern identified in published studies in RANK/RANKL-knockout mice. Anti-denosumab antibodies were detected in 66% of treated animals in the study and neutralising antibodies in 34% but mainly in animals in the lower dose groups. Antibody development caused a significant decrease in exposure at the lower dose levels, but not at the high-dose level.

Pregnancy categorisation

The sponsor proposes Pregnancy Category C, largely reflecting findings of developmental defects in RANK/RANKL knockout mice reported in the literature. However, given that one of these, lymph node agenesis, represents an irreversible effect, **Category D** is considered to be appropriate for denosumab. Furthermore, the reversibility of inhibition of bone development and tooth eruption associated with RANKL inhibition has also not been examined.

Paediatric use

The proposed indications for denosumab do not include paediatric use. No repeat-dose toxicity studies in juvenile animals were conducted. As noted above, the literature reports that RANK/RANKL knock-out mice had a failure of tooth eruption. In a study in 2-week old neonate rats, rat OPG-Fc at 10 mg/kg exhibited reduced bodyweight, bone growth and inhibition of tooth eruption. Given this result, appropriate cautionary statements in the Product Information regarding the use of denosumab in paediatric patients are warranted.

Local tolerance

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

Other studies

Immunogenicity

Immunogenicity was evaluated as part of the general toxicity studies. Denosumab was immunogenic with anti-denosumab antibodies detected in animals in all studies. The effect of these antibodies was to decrease the serum concentration of denosumab, particularly at the lower dose levels, and to reduce the pharmacodynamic response in some animals, as evidenced by the reduction in serum bone resorption markers. The development of antibodies in the nonclinical species, however, did not compromise the safety assessment of denosumab.

Immunotoxicity

No specific studies to examine immunotoxicity were conducted; however, no adverse effects on the functioning of the immune system were noted in the repeat-dose toxicity studies or in the 16-month pharmacology study in cynomolgus monkeys, based on the examination of immunoglobulin levels, immunophenotyping of lymphocytes, the T-cell dependent antibody response and/or the histopathology of lymphoid tissues.

Tissue cross-reactivity

Tissue cross-reactivity was evaluated in assays using human, monkey, rat and rabbit tissue. Immunoreactivity was noted in human and monkey lymph nodes as well as in rabbit lymph nodes and in rat bone. This is consistent with recognition of the primary pharmacological target, RANKL.

Nonclinical Summary and Conclusions

The pharmacology, pharmacokinetics and toxicity of denosumab were generally adequately examined in the submitted nonclinical studies and there were no major deficiencies. Toxicity studies were conducted with denosumab in cynomolgus monkeys only as rodent species are unsuitable due to their lack of pharmacodynamic responsiveness to denosumab owing to the species specificity of the antibody.

Primary pharmacology studies, showing inhibition of bone resorption and increased bone mass, density and mechanical strength in denosumab-treated monkeys, support the use of this pharmaceutical for the proposed indications.

Findings in the repeat-dose toxicity studies were consistent with the product's pharmacological effects on bone only. The pivotal study, of 12 months duration in monkeys, establishes a NOAEL of 50 mg/kg for once monthly SC administration. Exposure at this dose was a very high multiple of that in humans at the recommended clinical dose (150-times). Of note given the role of the RANK/RANKL system in immune function, immunotoxicity was not observed in any of the studies.

The monkey embryofetal developmental toxicity study revealed no treatment-related adverse effects up to a high multiple of the clinical exposure (~100). The predictive power of the study is limited by the small number of fetuses available for examination. Concerns stemming from findings of lymph node agenesis and failure of lactation reported in the literature for RANK/RANKL-knockout mice were not addressed in studies with denosumab. However, appropriate warnings are contained in the proposed PI document.

The absence of studies investigating the genotoxicity and carcinogenicity of denosumab is acceptable.

There are no nonclinical objections to the registration of denosumab for the proposed indications.

IV. Clinical Findings

Introduction

Clinical study data for evaluation included four bioavailability and bioequivalence study reports, six pharmacokinetic and initial tolerability study reports, one intrinsic factor pharmacokinetic report, two population pharmacokinetic reports, and three pharmacodynamic and pharmacokinetic studies. Reports for a further seventeen clinical trials of efficacy and/or safety were also included, of which four studies are considered pivotal to the indications being sought.

Pivotal efficacy data was generated from one Phase III trial (Study 20030216), a trial of denosumab in the treatment of postmenopausal osteoporosis. A further two Phase III trials (Study 20040135 and Study 20040138) provided pivotal efficacy data in support of denosumab in the treatment of bone loss in patients undergoing hormone ablation for breast and prostate cancer respectively. Longer-term efficacy data was provided from two Phase III open-label extension studies (Study 20050233 and Study 20060289). The effects of treatment discontinuation were examined in Study 20040132. A number of non-pivotal studies were submitted in support of the proposed indication, including one examining denosumab in postmenopausal women with bone loss (Study 20040132), three examining transition from treatment with alendronate or comparison with alendronate therapy (Study 20050141, Study 20050179 and Study 20050234), one examining satisfaction with therapy (Study 20060232), and one assessing immunogenicity (Study 20060237). Five Phase II studies of denosumab use for indications other than those proposed were submitted, including the drug's use in rheumatoid arthritis (Study 20040144), breast cancer with bony metastasis (Study 20040113), cancer with previous zoledronate treatment (Study 20040114) and relapsed or plateau-phase multiple myeloma (Study 20050134).

Pharmacodynamics

Mechanism of Action

Bone remodelling is the process by which old bone is resorbed by osteoclasts and new bone is formed by osteoblasts. One of the molecular mediators of bone resorption is osteoprotegerin (OPG), a member of the tumour necrosis factor receptor (TNFR) superfamily. Osteoprotegerin inhibits the development of bone-resorbing cells (osteoclasts) by binding to and inactivating RANK ligand (a receptor activator of nuclear factor kappa B). The antiresorptive effects of OPG suggest that an antibody that mimics the action of OPG has potential as a therapeutic agent in all bone diseases characterized by excessive bone resorption, such as primary osteoporosis, associated with increased osteoclast activity and differentiation.

Denosumab is a fully human monoclonal antibody with a high affinity for RANK ligand, the activator of osteoclastic activity that causes bone resorption. When denosumab binds to RANK ligand, the binding of RANK ligand to RANK is blocked, leading to prevention of terminal differentiation and activation of osteoclasts.

Results from Pharmacokinetic / Pharmacodynamic Studies

In the majority of pharmacokinetic (PK) studies, some measures of pharmacodynamic (PD) effects of the drug were evaluated simultaneously. These measures consisted of bone turnover marker assessments. Biochemical markers of bone resorption include NTX which measures cross-linked N-terminal collagen fragments in urine or serum.[44] These are products

[44] Cross-linked N-telopeptides of type I collagen (NTX or NTx) are a specific breakdown product of the type-I collagen found in bone cartilage, used as a marker of bone turnover.

of the proteolytic process of bone resorption brought about by osteoclasts. They show a greater increase at menopause than many other resorption markers and a greater degree of suppression when used to monitor the effects of antiresorptive agents. The urine NTX assay was corrected for urine levels of creatinine [NTX/creatinine nmol of bone collagen equivalents/mmol creatinine (nmol/mmol)]. Bone Formation Markers were also determined. These were bone-specific alkaline phosphatase (BSAP) a major osteoblastic product and it is a sensitive index of the rate of bone formation, abnormal bone turnover in patients with many metabolic disorders and effects of antiresorptive drugs on bone turnover.

In a Phase II, multicenter, randomized, placebo-controlled, double-blind, dose escalation study in postmenopausal women, the effects of single and repeated dose of denosumab on bone markers were examined. Across all cohorts, mean NTX/creatinine decreased by an average of approximately 50% to 80% from baseline, consistent with changes in mean serum NTX, which decreased by an average of approximately 30% to 60%. In the placebo group, mean NTX/creatinine and mean serum NTX remained near baseline levels throughout the study. The single dose cohorts were observed for 169 days and some single dose cohorts as well as multiple dose cohorts for 253 days. An additional 12 week follow-up period was completed for all but 9 subjects (4 SC, 5 IV) who withdrew consent. The delayed decrease in mean BSAP is consistent with denosumab acting primarily as a bone anti-resorptive agent and that coupling at the basic multi-cellular unit (BMU) level remained intact. BSAP decreased in a dose-dependent manner and levels remained below baseline throughout the study for most of the active drug treated subjects compared with the placebo group, in which mean BSAP remained near baseline during the study. Transient decreases in mean albumin-adjusted serum calcium and phosphorus occurred. Mean albumin-adjusted serum calcium remained within 10% of baseline throughout the study for both groups. Because of the decrease in serum calcium, a compensatory increase in mean intact parathyroid hormone (iPTH) occurred that returned to baseline levels over time.

A similar study was conducted in Japanese women with breast cancer related bone metastasis who received either 60 or 180 mg of denosumab as a single dose or 60 mg every four weeks for three doses. Median urinary NTX (uNTX)/Cr value decreased by 70.1% in Cohort 1 (60 mg single dose) and 67.1% in Cohort 2 (180 mg single dose) from baseline by Day 2 (approximately 24 hours post-dose). In Cohort 3 (60 mg every 4 weeks for 3 doses), no observations were planned on Day 2, but the median value decreased by 39.5% by Week 2, the earliest observation in this cohort. The median values of percent change from uNTX/Cr baseline at Day 85 were minus 90.8%, minus 61.1% and minus 60.0% in Cohorts 1-3, respectively. Cohort 1 had a higher median baseline uNTX/Cr than cohorts 2 and 3, which likely contributed to a larger percent reduction of uNTX/Cr. For other bone turnover markers such as type 1 serum C-telopeptide (sCTX1), BSAP and osteocalcin (OC), the profiles of suppression seemed comparable with that of uNTX. No skeletal related events (SRE) (for example, pathological bone fractures, spinal cord compression) occurred during the study.

The effect of denosumab on bone mineral density (BMD) in 412 post-menopausal women was evaluated in a randomised, placebo controlled study. The drug was to be administered for up to 4 years, but preliminary data were reported. In the first 24 months, increases in BMD of the lumbar spine were observed in all denosumab treated cohorts (range: 3.9% to 8.8%) compared with a 1.3% decrease for placebo. Bone mineral densities of the total hip, distal 1/3 radius, total body (without head), femoral neck, and trochanter increased steadily at each time point and were greater for all denosumab dose cohorts than placebo through Month 24. Across denosumab dose cohorts, the magnitude of the increase in BMD was similar with the exception of the 14 mg every 6 months dose cohort. Denosumab treatment resulted in rapid and sustained decreases in bone turnover markers sCTX1, uNTX/Cr, and BSAP through

Month 24. In the first 12 months, the magnitude of suppression among denosumab-treated cohorts was up to 89% for sCTX1, 73% for uNTX/Cr, and 75% for BSAP. At Month 24, these decreases were 73% for sCTX1, 50% for uNTX/Cr, and 58% for BSAP. Across the denosumab dose cohorts, the maximal suppression of bone turnover markers was similar. In the lower dose cohorts, the bone turnover markers tended towards baseline levels before the next dose.

The effects on bone markers were also evident in single dose (0.03-3.0 mg/kg) pharmacokinetic studies. In a dose ranging study in post menopausal women, there was significant suppression of uNTX/Cr compared to placebo ($p < 0.05$). The effect had a rapid onset with significant decreases by Day 2. The mean maximal suppression ranged from 50% (0.03 mg/kg) to 82% (3 mg/kg). Measures of sCTX1 were suppressed in a similar manner. In healthy men aged more than 50 years, doses of denosumab from 0.1 to 3.0 mg/kg produced a suppression of uNTX/Cr compared to placebo ($p < 0.05$). The effects were independent of the age of the subjects. Furthermore there was a positive effect on BMD.

Rapid and sustained changes in uNTX/Cr as well as sCTX1 were also observed in single dose ranging studies for post menopausal Japanese women and in both men and women with cancer related bone metastases. In each of these studies the doses of denosumab ranged from 0.1 to 3.0 mg/kg.

An open-label, single-dose study was performed to evaluate changes in serum calcium when transitioning postmenopausal women with low BMD from alendronate (70 mg weekly or equivalent) to a single dose of denosumab. Fourteen days after dosing, the mean percent change from baseline in sCTX1 concentration was approximately minus 60% and minus 73% for subjects in the 15 mg and 60 mg denosumab groups, respectively. These changes were generally maintained from Day 14 through to Day 84. The mean percent change from baseline for sCTX1 for subjects who continued on alendronate treatment ranged from approximately minus 40% to 20%, with no change, on average at Day 107.

Population Pharmacodynamics Analysis

A population pharmacodynamic analysis was performed and included sCTX1 and/or lumbar spine BMD data from a total of 13 clinical studies including healthy subjects, postmenopausal women, and subjects with cancer. Index and test data subsets were prepared and used to develop and evaluate the population pharmacodynamic model. The Index dataset included data from 2216 subjects. Denosumab was administered as a single (N = 204) or multiple (N = 1605) SC dose ranging from 0.01 to 3.0 mg/kg or 6 to 210 mg administered every 4 weeks, 3 monthly or 6 monthly for up to 48 months. The Test data used to externally evaluate the model included data from 7868 subjects. The 3916 subjects received denosumab 60 mg SC 6 monthly. The mean (range) age and body weight were 71 (28 to 91) years and 64 (33 to 140) kg, respectively, and 118 of 10,084 subjects (1.17%) were men. The population consisted of 89%, 6.9%, 3.3% and 1.0% Caucasian, Hispanic, Asian and Black subjects, respectively. A complex turnover pharmacodynamic model was developed that described the time course of sCTX1 and BMD changes for denosumab dose-response and, in particular, for 60 mg 6 monthly dosing. The model described the rapid, dose-dependent, and reversible effects of denosumab on sCTX1. A maximum reduction in sCTX1 of 91% was estimated, and reductions (>55%) were sustained throughout the dosing interval. The model also described the association between these reductions in sCTX1 and the continuous increases in lumbar spine BMD. Based on the covariate analysis, body weight, age, race, disease status (healthy subjects, postmenopausal women with osteopenia or osteoporosis, or subjects with cancer), or treatment with aromatase inhibitors do not impact the pharmacodynamic effects of denosumab. Thus, dose adjustments are not warranted based on these covariates. The

variability in the pharmacodynamic parameters of denosumab appeared to be moderate to high. The means and distributions for changes in sCTX1 and BMD profiles following SC administration of 1 mg/kg versus 60 mg every 6 months for 4 years are highly comparable as demonstrated through simulation analysis.

Summary of Pharmacodynamics

Denosumab is a human monoclonal antibody with a high affinity for RANK ligand. Data suggesting reduced bone resorption in the PD studies would suggest an effect on RANKL.

Single and repeated doses of denosumab had favourable effects on bone turnover markers which were long lasting (up to 6 months).

A population pharmacodynamic model predicted that the covariates body weight, age, race, disease status, or treatment with aromatase inhibitors would not affect the pharmacodynamic effects of denosumab, although this was not verified in the Phase II PD studies.

Pharmacokinetics

Single-dose PK Studies

The absorption of denosumab following subcutaneous injection was relatively rapid but prolonged in the 5 single dose pharmacokinetic studies. In a single dose study in 46 post menopausal women who received increasing single doses of denosumab, concentrations of the drug were detectable as soon as 5 minutes after the dose. On the other hand C_{max} was not achieved until 7 to 10 days after the dose. Furthermore, C_{max} values were not dose proportional in this study. Similar results were observed in a study of Japanese post menopausal women receiving denosumab doses as a single subcutaneous injection. Serum concentrations of the compound were detected within an hour of dosing but C_{max} was not observed until 7 to 14 days after the dose and the C_{max} was not dose proportional (Table 4). In an escalating dose study in men aged more than 50 years, plasma concentrations of denosumab were detected within 24 hours of the dose. In this study, the time to C_{max} was highly variable ranging from 3 to 14 days after injection; however, median time to C_{max} was between 7 and 10 days across the dose ranges studied. There is no difference in the median or range between men and women at those doses. C_{max} was approximately linearly proportional to the dose. Denosumab demonstrated rapid but prolonged absorption in patients with bone metastasis secondary to breast cancer or multiple myeloma. After a single dose, plasma concentrations of the compound were evident at 1 hour with C_{max} occurring between 14-21 days post dose in the breast cancer group. For patients with multiple myeloma, the time to C_{max} was more variable (7-21 days). This pattern of absorption was also evident in 20 female patients who were switched from alendronate to denosumab. Time to maximum concentration ranged from 14-21 days (15 mg SC dose) or from 3-28 days (60 mg SC dose).

As denosumab is designed for subcutaneous injection the effect of food on absorption is not relevant.

Table 4: Pharmacokinetic Parameters of Denosumab after Single Doses (by different routes of administration)

Subcutaneous Route					
Parameters	0.03 mg/kg	0.1 mg/kg	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Tmax (h)*	7 (5-14)	7 (3-14)	14 (7-56)	17.5 (7-42)	10 (5-42)
Cmax (ng/mL)	157 ± 67.3	721 ± 103	2230 ± 873	8990 ± 3340	36200 ± 7280
t½β (days)	23.3 ± 2.44	19.5 ± 3.15	33.2 ± 9.5	30.2 ± 7.04	29.5 ± 5.46
AUC 0-∞	3.77 ± 2.04	20.4 ± 4.08	115 ± 42.1	538 ± 224	2070 ± 483

(µg.day/mL)					
Cl/F (mL/h/kg)	0.520 ± 0.403	0.212 ± 0.0441	0.127 ± 0.0558	0.0897 ± 0.0356	0.0634 ± 0.0146
Intravenous Route					
Parameters	0.03 mg/kg	0.1 mg/kg	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Tmax (h)*	0 (0 to 0.17)	0 (0 to 0.04)	0.021 (0 to 0.04)	0 (0 to 0.04)	0.04 (0 to 0.17)
C0 (ng/mL)	1040 ± 36.5	3830 ± 779	10600 ± 1730	35200 ± 10400	110000 ± 26600
t½β (days)	8.29 ± 1.16	12.7 ± 3.30	24.4 ± 5.83	35.1 ± 4.96	37.3 ± 6.96
AUC 0-∞ (µg.day/mL)	6.00 ±.729	33.7 ± 5.71	180 ± 48.3	688 ± 195	2760 ± 738
Cl (mL/h/kg)	0.190 ± 0.0213	0.127 ± 0.0228	0.0750 ± 0.0244	0.0644 ± 0.0189	0.0495 ± 0.0193
Vss mL/kg	33.9 ± 3.94	39.9 ± 7.15	44.9 ± 7.13	54.1 ± 5.67	54.5 ± 9.70

* Data for Tmax is median and range; all other data mean ± SD.

Multiple Dose Pharmacokinetics

Two of the multiple dose studies with denosumab were designed primarily as efficacy studies and kinetic determination was a secondary objective. Post menopausal women received two doses of denosumab 0.1 mg/kg at a 3 month interval and the kinetic profile determined for each. The kinetic parameters in both of the intervals were not significantly different and accumulation was not apparent. Denosumab pharmacokinetics following multiple dosing did not appear to be different from that following a single dose.

After repeated doses every 4 weeks of denosumab in Japanese females with breast cancer, absorption was rapid, with maximal concentrations observed at 8 to 10 days after a single dose and at 14 to 18 days after a repeated dose. For the repeated dosing regimen, an approximate 2.2 fold accumulation was observed by the third dose relative to the first.

The effect of denosumab on bone mineral density was evaluated at different doses and different administration schedules in 406 patients. Non-linear pharmacokinetics were apparent across both the 6 to 30 mg every 3 months and 14 to 210 mg every 6 months dose ranges, with exposure based on mean area under the concentration time curve calculated from time zero to the end of the dosing interval at steady state ($AUC_{0-\tau}$) values increasing greater than dose-proportionately (~10- and 36-fold for the 5- and 15-fold increases in dose, respectively). However, mean $AUC_{0-\tau}$ values increased approximately dose-proportionately between the 60 and 210 mg every 6 months doses. Additionally, exposure based on mean C_{max} values increased approximately dose-proportionately across both the every 3 months and every 6 months dose ranges. C_{max} values were generally observed in median times of less than 1 week for the every 3-month dose groups and between 2 and 3 weeks for the every 6-months dose groups. No marked (> 2-fold) accumulation was observed for any dosing regimen. For the 60, 100, and 210 mg dose groups, mean half-life ($t_{½}$) values that described the disposition of denosumab over large proportions of exposures (based on AUC) and the every 6-month dose intervals were similar, ranging from approximately 25 to 34 days. For both the every 3-months and every 6-months dose schedules, mean exposures were comparable (< 20% different) between the first and subsequent doses, indicating a lack of change in denosumab pharmacokinetics with time or upon multiple dosing (Table 5).

The effect of denosumab on lumbar spine bone mineral density was investigated in Japanese post menopausal women. Subjects received 14, 60 or 100 mg twice separated by six months and were followed up to 12 months after the first dose. For the 7.2-fold increase in denosumab dose from 14 to 100 mg, exposure based on mean C_{max} values increased approximately dose-proportionally (7.2- to 7.7-fold). Mean $AUC_{0-\tau}$values increased greater

than dose-proportionally from 14 to 60 mg (5.4 to 7.0-fold for the 4.3-fold increase in dose). However, mean $AUC_{0-\tau}$values increased approximately dose-proportionally from 60 to 100 mg (1.7- to 1.8-fold for the 1.7-fold increase in dose). No accumulation was observed at any dose level, with mean accumulation ratios of 0.961 to 1.14. Although pharmacokinetic sampling times differed between the first and second doses, the mean C_{max} and $AUC_{0-\tau}$values differed by < 28% between the first and second doses for each dose regimen, consistent with a lack of change in denosumab pharmacokinetics with time or multiple dosing.

Table 5: Denosumab PK with Multiple Dosing

Table 10-1. Mean (SD) Denosumab Pharmacokinetic Parameters Following Administration of 6, 14, or 30 mg Denosumab Every 3 Months

Dose (mg)	Dose number	T_{max}[a] (day)	C_{max} (ng/mL)	AUC_{0-tau} (day•µg/mL)	C_{min} (ng/mL)	AR
6	1	3.0 (2.9 – 32)	554 (244)	17.4 (8.54)	2.25 (9.80)	1.23
	3	3.9 (1.9 - 35)	638 (276)	20.6 (11.4)	2.36 (5.23)	
14	1	4.0 (2.8 - 39)	1450 (621)	60.3 (25.5)	58.2 (87.2)	1.27
	3	27 (2.0 - 93)	1550 (693)	68.3 (34.5)	97.2 (144)	
30	1	5.0 (2.9 - 34)	3540 (1590)	170 (87.5)	446 (360)	1.04
	3	4.0 (1.9 - 37)	3760 (1830)	193 (108)	799 (720)	

[a] Median (range)

T_{max} = time of maximum observed serum denosumab concentration (C_{max})

AUC_{0-tau} = area under the serum denosumab concentration-time curve over the dosing interval

C_{min} = trough serum denosumab concentration

AR = accumulation ratio

Dose-proportionality of denosumab pharmacokinetics

In both single and multiple dose studies, the proportionality of denosumab kinetics was evaluated. Following single IV doses of the drug in the range 0.01 to 3.0 mg/kg, the area under the plasma concentration time curve from zero time to infinity ($AUC_{0-\infty}$) increased more than dose proportionately. In the same study, single SC dose administered over the same dose range also showed similar results with greater than dose proportional increase in drug exposure. In this study, C_{max} value also did not exhibit proportionality to the dose. Non-linear pharmacokinetics were also observed in other single dose studies using SC administration over the same dose range. Overall results from these studies suggest that denosumab demonstrates non-linear pharmacokinetics.

Absorption, Distribution, Metabolism and Excretion Profile

Absorption

Following subcutaneous administration of denosumab, absorption is relatively rapid and prolonged with serum concentrations detected within one hour of dosing but C_{max} not observed until 7-14 days after dosing.

Distribution

Denosumab was administered intravenously in a single dose escalation study to 36 post menopausal women. In this study a separate group of 34 women received a single subcutaneous dose over the same dose range: 0.01 to 3.0 mg/kg. After the IV dose the volume of distribution was 28.9 to 54.5 mL/kg. This volume is similar to that of total body water suggesting that the compound is not distributed widely outside of the vasculature. Based on a comparison with corresponding doses administered IV the bioavailability of the SC doses ranged from 35.6% to 77.9%.

Metabolism

Denosumab is made up of amino acids and carbohydrates similar to immunoglobulin and is unlikely to be eliminated by hepatic metabolic pathways. Based on non-clinical data, its metabolism and elimination would be expected to follow the immunoglobulin clearance pathways resulting in degradation to small peptides and individual amino acids.

Elimination

Denosumab is slowly eliminated from the plasma. Following administration of single IV doses of denosumab, the elimination half-life increased with dose. Thus at 0.03 mg/kg, the mean elimination half-life was 8.29 ± 1.16 days which progressively increased to 37.3 ± 6.96 days at 3.0 mg/kg. A similar phenomenon of increasing half-life was observed after SC administration but was not as pronounced as for IV The mean half-life following SC administration of denosumab 0.03 mg/kg and 3 mg/kg was 23.3 days and 29.5 days, respectively. This dose dependence is reflected in the corresponding data for clearance: mean clearance was 0.190 ± 0.0213 mL/h/kg and 0.0495 ± 0.0193 mL/h/kg after IV dosing for 0.03 mg/kg and 3 mg/kg, respectively. For SC dosing, clearance is also decreased with dose. Thus at 0.03 mg/kg the mean apparent clearance was 0.520 ± 0.403 mL/h/kg and at 3.0 mg/kg it was 0.0634 ± 0.0146 mL/h/kg.

Kinetics in Special Populations

Effect of Renal / Hepatic Dysfunction on Denosumab Pharmacokinetics

The effects of varying degrees of renal dysfunction on the pharmacokinetics of denosumab were evaluated in an open label single dose study. Subjects were assigned to a renal function group based on creatinine clearance (CrCL) as calculated by the Cockcroft-Gault equation. There were five groups studied:

Group 1: Normal renal function (CrCL > 80 mL/min); 12 subjects
Group 2: Mild chronic kidney disease (CKD) (CrCL 50 to 80 mL/min); 10 subjects
Group 3: Moderate CKD (CrCL 30 to 49 mL/min); 10 subjects
Group 4: Severe CKD (CrCL < 30 mL/min); 7 subjects
Group 5: End-stage renal disease (ESRD) requiring haemodialysis; 7 subjects

All subjects received a single injection of denosumab of 60 mg subcutaneously. Blood samples were collected for pharmacokinetic and pharmacodynamic analyses at specified time points from pre-dose through Day 113 after receiving denosumab. The pharmacokinetic profile of denosumab was not significantly affected by the degrees of renal impairment. Mean differences in $AUC_{0\text{ -16 weeks}}$ and C_{max} values between the renal impairment groups and the normal controls were small compared to the inter-individual differences in exposure observed between subjects within the various groups. Parametric and nonparametric analyses did not indicate any statistically significant relationship between renal function and pharmacokinetic parameters of denosumab. Impairment of renal function did not appear to alter the single dose kinetics of denosumab. Effects of hepatic impairment on denosumab pharmacokinetics were not evaluated.

Effect of Age and Gender

Some indication of the effects of age on the pharmacokinetics (and pharmacodynamics) of denosumab were available from an escalating dose study in men aged more than 50 years. In this randomised, placebo-controlled study, subjects received 0.1, 0.3, 1.0, 3.0 mg/kg or placebo as a single subcutaneous injection. Subjects were stratified according to age: 50-64 years or ≥65 years. Although the report states there was no effect of age on either kinetic or dynamic responses, there was no specific statistical analysis to support this statement. However, the conclusion of a lack of age effect is supported by the population kinetic analysis (see below).

There were no direct comparisons of data for males and females either in healthy subject or patient populations. Although not derived from a properly constituted study or strictly comparable statistically, the data suggests that men and women do not differ in kinetic handling for denosumab.

Bioequivalence Studies with Denosumab

Four studies were conducted in healthy volunteers to assess the bioequivalence of different formulations of denosumab. Both pharmacokinetic and pharmacodynamic equivalence was assessed in these studies. All studies were conducted as open label evaluations in male and female volunteers following single doses of denosumab administered subcutaneously.

In the first study, a total of 148 subjects (74 per group) were assessed during a 21-day screening period. Eligible subjects received a 60 mg injection of denosumab from either a graduated syringe (GS) or a pre-filled syringe (PFS) (the proposed marketing devices are a 1 mL single-use pre-filled syringe or 1 mL vial) and were then followed for 17 weeks after the dose. The post dose sampling period was 16 weeks during which time blood samples were collected for analysis of denosumab and serum C-telopeptide (sCTX) at regular intervals. Pharmacokinetic parameters were calculated using model independent methods and the geometric ratio for C_{max} and $AUC_{0\text{-}16weeks}$ between the two devices calculated. Mean serum concentrations of denosumab across time for both devices were nearly superimposable. The point estimate for the PFS: GS ratio of geometric means for $AUC_{0\text{-}16weeks}$ was 1.04 and the 90% confidence interval for the ratio was 0.94 to 1.14. For the geometric ratio of C_{max} the point estimate was 1.05 and the 90% confidence interval were 0.96 to 1.14. On this basis it was concluded that the two devices were bioequivalent from a pharmacokinetic point of view, as the ratios were within the accepted bioequivalence limits of 0.80 to 1.25. From a pharmacodynamic perspective, bioequivalence was assessed by the effect of denosumab on sCTX. Mean decreases in the peptide from baseline concentrations were similar for both devices: 84.6% for PFS and 86.1% for GS. The point estimate for the PFS: GS ratio of geometric means for $AUEC_{0\text{-}16\ weeks}$ was 0.98, and the 90% confidence interval (CI) was 0.95 to 1.02. The median $t_{max,}$ sCTX was 17.5 days for denosumab PFS and 21 days for denosumab GS, ranging from 2 to 112 days for both groups. These pharmacodynamic results also support the bioequivalence of denosumab PFS and denosumab GS.

A similar open evaluation was performed in 122 healthy volunteers (61 per group) to examine the bioequivalence of formulations of denosumab manufactured at two different plants. The pharmacokinetic and pharmacodynamic results supported the bioequivalence of denosumab from the two plants.

Using an open, parallel group study, the bioequivalence of two formulations of denosumab manufactured at one of the above sites and another site was evaluated. Again, the pharmacokinetic and pharmacodynamic data supported the bioequivalence of the two formulations.

An open, parallel group evaluation was performed in 116 healthy volunteers (58 per group) to assess the bioequivalence of denosumab administered as subcutaneous injections of 120 mg. In this study denosumab was administered as two 1.0 mL injections of a 60 mg/mL solution (treatment A) or as a single injection of 1.7 mL of a 70 mg/mL solution (treatment B). Again the pharmacokinetic and pharmacodynamic data supported the bioequivalence of the two regimens.

These four studies suggest both pharmacokinetic and pharmacodynamic equivalence between different formulations of denosumab manufactured at different sites as well as for different volumes of injection.

Pharmacokinetics in Special Populations

A population pharmacokinetic study was performed for denosumab**.** The analysis included denosumab serum concentration-time data from a total of 14 clinical studies (6 Phase 1 studies, 5 Phase II studies and 3 Phase III studies) including healthy and cancer subjects, and postmenopausal women with osteopenia or osteoporosis. In these studies, denosumab was administered as a single intravenous (N=36 subjects) or a single subcutaneous (N=175 subjects) dose or as multiple subcutaneous doses (N=1560 subjects). The doses of denosumab ranged from 0.01 to 3 mg/kg (or 6 to 210 mg) and were given every 4 weeks or every 3 months or every 6 months for up to 48 months. Index and Test data subsets were prepared and used to develop and evaluate the model. The Index data consisted of six Phase I studies, five Phase II studies and two Phase III studies. The Test data used to externally evaluate the model included data from one Phase III study of serum samples from 420 postmenopausal osteoporotic women.

A two-compartment open model with first order absorption, parallel linear and capacity-limited elimination best characterized denosumab pharmacokinetics using NONMEM VI software. The model was parameterized in terms of clearance and volume of distribution. Denosumab SC bioavailability was 61% and the mean absorption time was 7 days. After IV administration, the distribution half-life was 2 days. The volume of distribution at steady state was 3.8 L. The linear clearance, likely through non-specific catabolism, was 3 mL/hr and parameters for target-mediated (non-linear) elimination were V_{max} 3.1µg/hr and Km 216ng/mL. Age and treatment with aromatase inhibitors had no discernable impact on the denosumab pharmacokinetics. Subjects with solid tumours, Blacks and Hispanics had 110%, 51% and 56% higher linear clearance, respectively, relative to Caucasian postmenopausal women; however, based on simulations, these differences did not appear to be clinically important. Between subject variability was ~ 40% for absorption rate, volume of distribution and linear clearance. The integration of denosumab pharmacokinetic data from 14 clinical studies demonstrated time independent non-linear pharmacokinetics. The pharmacokinetic impact of body weight, patient population and race is likely limited, given the moderate inter-individual pharmacokinetic variability; thus, dose adjustments on the basis of the covariates assessed are not warranted.

Pharmacokinetics Summary

Denosumab appears in plasma soon after subcutaneous injection (within an hour) but maximum plasma concentration are not achieved for several days. The bioavailability of denosumab SC is between 35% and 79% of an IV formulation. Denosumab exhibits non-linear kinetics. Denosumab kinetics for the multiple doses did not appear to be different from that for a single dose.

Denosumab is not extensively distributed to the tissues. The volume of distribution of denosumab approximates that of total body water.

Denosumab elimination is dose dependent with a plasma half life of elimination of about 30days at clinically recommended SC doses.

Varying degrees of renal dysfunction including end stage renal disease do not affect the single dose kinetics of denosumab.

Age and gender did not appear to significantly alter denosumab kinetics.

An injection (60 mg) of denosumab from a graduated syringe (GS) or from a pre-filled syringe (PFS) was bioequivalent. Denosumab administered as two 1.0 mL injections of a 60 mg/mL solution or as a single injection of or 1.7 mL of a 70 mg/mL solution were bioequivalent.

A two-compartment open model with first order absorption, parallel linear and capacity-limited elimination best characterized denosumab pharmacokinetics by population kinetic modelling. The pharmacokinetic impact of body weight, patient population and race is predicted to be limited using the population kinetic model.

Efficacy

Two trials are considered pivotal to that part of the application which is discussed in this document. One Phase III trial (Study 20030216) examined the use of denosumab in the treatment of postmenopausal osteoporosis. One Phase III trial (Study 20040135) examined denosumab in the treatment of bone loss in patients receiving hormonal ablative therapy for breast cancer. Another Phase III trial (Study 20040138) examined denosumab in the treatment of bone loss in patients receiving hormonal ablative therapy for prostate cancer.

Longer-term efficacy data was provided from the Phase III open-label extension study (Study 20050233). An interim synopsis is provided of a third extension study (Study 20060289), which includes minimal efficacy data at this point but in the future will provide data on up to ten years of denosumab treatment.

Six non-pivotal studies were submitted in support of the proposed indication (Study 20040132, Study 20050141, Study 20050179, Study 20050234, Study 20060232 and Study 20060237). The submission also included five Phase II studies of denosumab use for indications other than those proposed (Study 20040144, Study 20040113, Study 20040114 and Study 20050134).

Pivotal Trials in Treatment of Post-Menopausal Osteoporosis

Study 20030216

Study Design and Patient Characteristics

This was a large Phase III international, multicentre, randomized double-blind placebo-controlled trial of the efficacy and safety of denosumab in reducing the risk of new fractures in women with PMO. Patients were randomized 1:1 in a double-blinded fashion to receive either placebo SC or denosumab 60 mg SC every six months for three years. The on-treatment phase therefore included six doses with follow-up to Month 36. In addition to the study drug, all patients received at least 1 g of daily calcium and at least 400 IU of daily vitamin D supplementation. Randomization was stratified by age at entry into four groups: 60 to 64 years, 65 to 69 years, 70 to 74 years, and greater than 75 years. The duration of the trial was from August 2004 to June 2008. The study was conducted in compliance with Good Clinical Practice (GCP) guidelines.

All enrolled patients had a lateral spine X-ray and DEXA at screening, 12, 24 and 36 months (or termination, if earlier). If available, vertebral fracture analysis (VFA) by DEXA was collected at baseline and at 6 months (or another lateral spine X-ray if the technology was

unavailable at the study centre). In addition to the main study, at some sites with particular areas of expertise (for example, bone biopsy or quantitative computerized tomography technology) patients were invited to participate in any of seven protocol-described substudies. These included a DEXA substudy, qualitative computed tomography (QCT) of the spine and hip substudy, QCT of the distal radius substudy, bone marker substudy, pharmacokinetic substudy, fracture healing substudy and bone biopsy substudy.

An enrolment of 7,200 patients was planned, with 3,600 in each treatment arm. Inclusion criteria were postmenopausal status, aged between 60 and 90 years, ambulatory and in good health, and a diagnosis of osteoporosis as defined by a bone mineral density (BMD) T-score of less than minus 2.5 at the lumbar spine, hip or both. Patients were excluded from the trial if they had a BMD T-score of less than minus 4.0 at the hip or spine. Patients using oral bisphosphonates for more than three cumulative years were excluded, but patients who had used oral bisphosphonates less than three years and had stopped more than a year ago (or had an exposure of less than three months) were eligible. Other treatments within the previous six months which excluded patients from the study were parathyroid hormone derivatives, steroids, systemic hormone replacement or selective oestrogen receptor modulators, calcitriol or calcitonin. A total of 7,868 patients were eligible and enrolled. At one European investigational site, a spot quality assurance audit by the relevant governmental agency identified a number of breaches of GCP guidelines, in particular with regard to record-keeping, the reporting of adverse events, informed consent procedures and oversight of study conduct. All 60 patients from this site underwent full early-termination procedures according to protocol and all 60 were withdrawn (prior to unblinding) from safety and efficacy analyses in order to mitigate the risk of confounding. The intention-to-treat (ITT) population therefore included 7,808 patients, of whom 3,902 received denosumab and 3,906 received placebo. Mean (±SD [standard deviation]) age was 72.3 ± 5.2 years. The large majority (92.7%) were white or Caucasian. The two treatment groups were well-matched for baseline demographics, as well as for calculated fracture risk according to the validated and widely-used WHO risk-estimating "FRAX" algorithm.[45] The groups were also well-matched for baseline fracture history and BMD T-scores.

On-study protocol deviations were more common for the placebo group (13.7%) than for denosumab (9.4%), largely due to an imbalance in exclusionary medications (particularly bisphosphonates) taken on study. It seems reasonable to agree with the investigators' argument that this effect would, if anything, reduce the apparent treatment effect of the study drug.

There were no significant differences in patient disposition between the two treatment groups; 630 patients (16.1%) discontinued study treatment from the denosumab arm, compared to 700 patients (17.9%) receiving placebo. Reasons for withdrawal were well balanced between the two groups. The most common reason overall was withdrawal of consent (747 patients, 9.6%). Withdrawals due to adverse events comprised 174 patients (2.2%). Only 114 patients (1.5%) were lost to follow-up.

The study was appropriately designed to provide at least 99% power to detect a 45% difference in the primary endpoint (vertebral fracture) using χ^2 tests of equal proportions at 36 months ($\alpha = 0.05$). Analyses were carried out on the ITT population, with the per-protocol (PP) population used in a number of cases as additional sensitivity analyses to demonstrate robustness.

[45] Kanis JA, et al. FRAX and the assessment of fracture probability in men and women from the UK. Osteoporosis International 2008 ; 19 : 385-397.

Primary Efficacy Outcomes

The primary efficacy measure was the incidence of a binary outcome (yes/no) of new vertebral fractures during the entire 36-month observational period. Vertebral fractures were determined by a pair of independent blinded radiologists using a validated semi-quantitative method.[46] Using this method, a new vertebral fracture was defined as an increase of at least one Genant Grade (from a previous grade of zero) in any vertebra from T4 to L4. New vertebral fractures were statistically significantly less common ($p < 0.0001$) in the denosumab group (86/3702 patients, 2.3%) compared to placebo (264/3691 patients, 7.2%) (Table 6). The finding remained statistically significant ($p < 0.0001$) when including worsening of existing fractures. This equated to an odds ratio of 0.31 (95% CI of 0.24 to 0.39). Sensitivity analyses confirmed the robustness of these findings using the full analysis subset, per protocol subset, and after controlling for a range of baseline covariates including time since menopause, lumbar spine T-score, and existing vertebral fracture. Indeed, statistically significant ($p < 0.0001$) risk reductions remained for all baseline subgroup characteristics analysed. The findings were apparent from the time of second measurement, at 12 months (Figure 3).

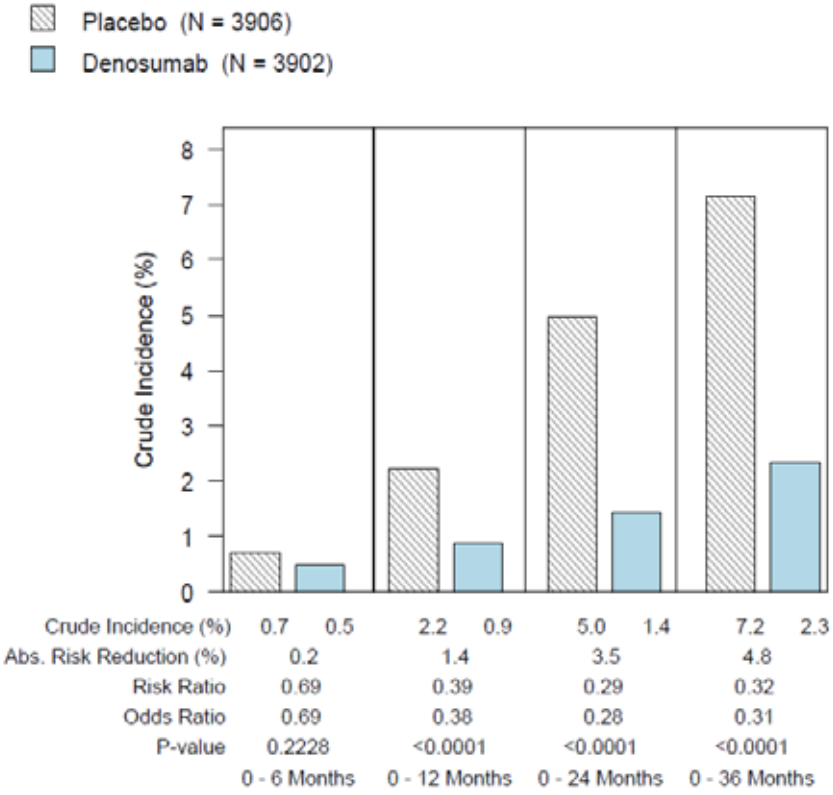
Table 6 - Incidence of new vertebral fractures at 36 months (Study 20030216)

	Crude Incidence		Risk Comparison Estimates						
			Absolute Risk Reduction (%)[a]		Risk Ratio[a]		Odds Ratio[b]		
	n/N1	%	Pt Est	(95% CI)	Pt Est	(95% CI)	Pt Est	(95% CI)	p-value
New vertebral fracture									
Placebo (N = 3906)	264/3691	7.2							
Denosumab 60 mg Q6M (N = 3902)	86/3702	2.3	4.8	(3.9, 5.8)	0.32	(0.26, 0.41)	0.31	(0.24, 0.39)	<0.0001

In a post-hoc analysis, using the reciprocal of the absolute risk reduction in new vertebral fractures between denosumab and placebo, the number needed to treat (NNT) over the three years of study was 20.7 (95% CI of 17.3 to 25.8).

[46] Genant HK, et al. Vertebral fracture assessment using a semiquantitative technique. J Bone Min Res 1993; 8: 1137-1148.

Figure 3 - Incidence of new vertebral fractures through Months 6, 12, 24 and 36 (Study 20030216)



Secondary Efficacy Outcomes

The secondary efficacy endpoints were time to first nonvertebral fracture and time to first hip fracture.

The crude incidence of nonvertebral fracture at 36 months was somewhat higher in the placebo group (293/3906 patients, 7.5%) compared to denosumab (238/3902 patients, 6.1%). The reduction in risk was significant ($p = 0.0106$) with an absolute risk reduction at 36 months of 1.5% (95% CI of 0.3% to 2.7%). Sensitivity analyses demonstrated a robust effect across the full analysis and per-protocol sets, and within a number of subgroup analyses. Kaplan-Meier plots (Figure 4) found separation of 95% confidence intervals from 24 months onward.

The crude incidence of hip fracture at 36 months was also higher in the placebo group (43/3906 patients, 1.1%) compared to denosumab (26/3902 patients, 0.7%). The risk reduction was moderately significant ($p = 0.0362$) with an absolute risk reduction at 36 months of 0.3% (95% CI of -0.1 to 0.7). Sensitivity analyses confirmed a robust effect in the per-protocol set. Kaplan-Meier plots (Figure 5) again found separation of the 95% confidence intervals from 24 months.

Figure 4 - Kaplan-Meier curve of time to first nonvertebral fracture (Study 20030216)

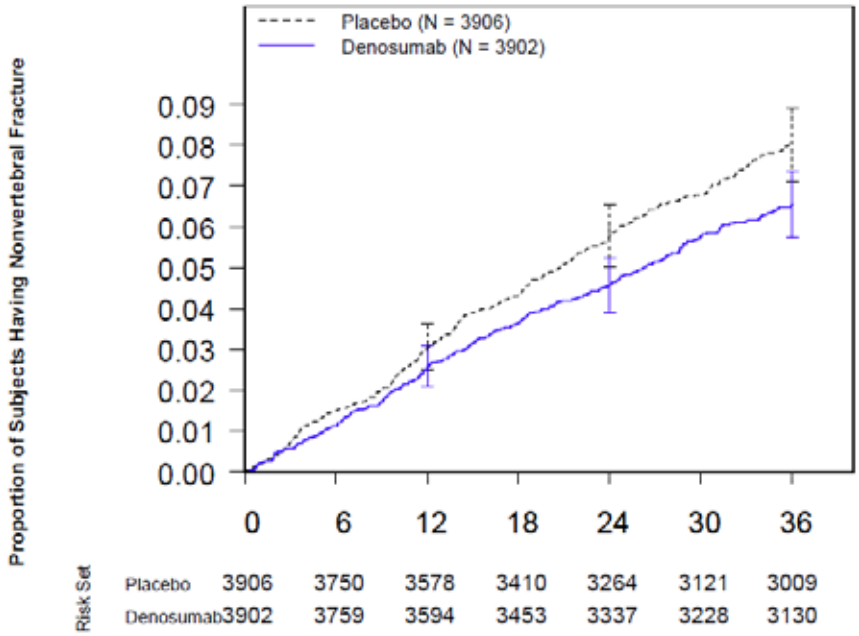
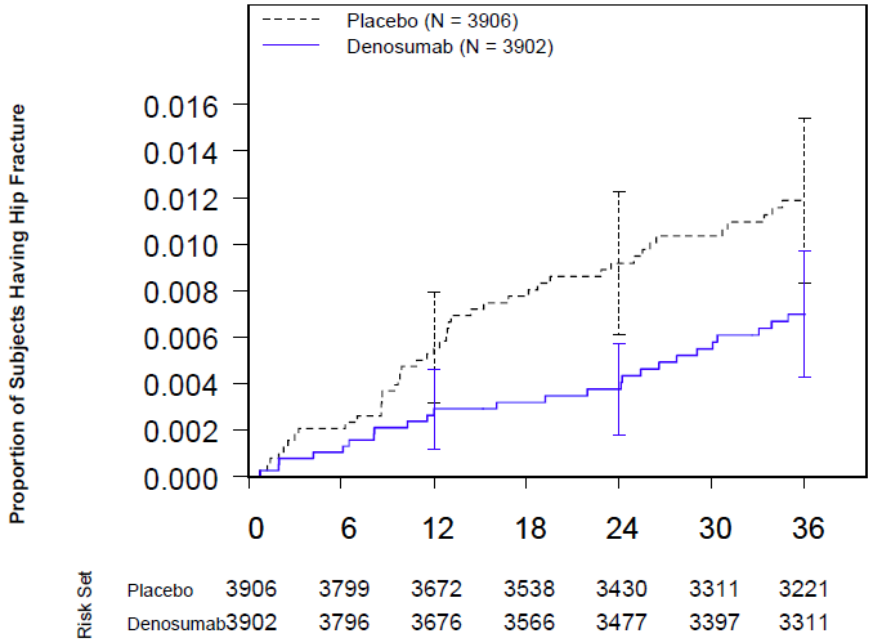


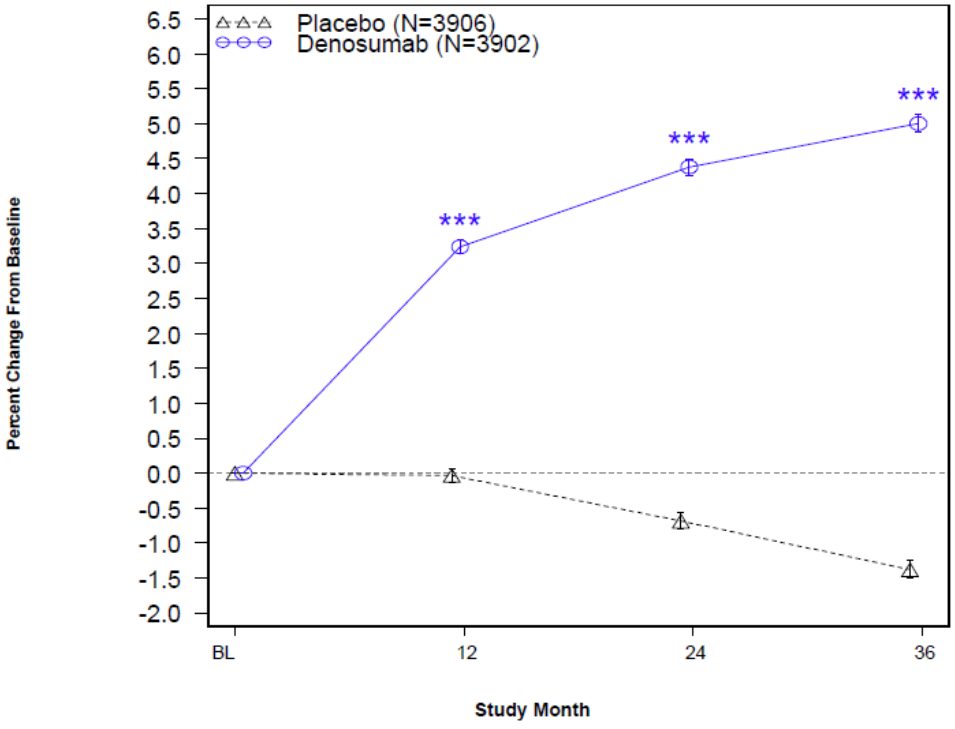
Figure 5 - Kaplan-Meier curve of time to first hip fracture (Study 20030216)



Tertiary Efficacy Outcomes and the Substudies

A statistically significant difference ($p < 0.0001$) in mean BMD of the lumbar spine was seen in the denosumab treatment group compared to placebo. The mean difference between the groups at 36 months was 8.8% (95% CI of 8.6% to 9.1%) in favour of denosumab. A difference in BMD at the total hip was also seen for denosumab over placebo, achieving statistical significance ($p < 0.0001$) for the time points at 12, 24 and 36 months (Figure 6), namely 3.3%, 5.1% and 6.4% in favour of denosumab.

Figure 6 - Total hip BMD percent change from baseline by visit (Study 20030216)



The 441 patients enrolled in the DEXA substudy were similar to the overall study population in terms of disposition, demographics and baseline disease characteristics. A statistically significant increase ($p < 0.0001$) in BMD was found at all sites for the denosumab group compared to placebo, including the lumbar spine (Figure 7), total hip (Figure 8) and total body BMD (Figure 9).

Figure 7- Lumbar spine BMD percentage change from baseline by visit (Study 20030216)

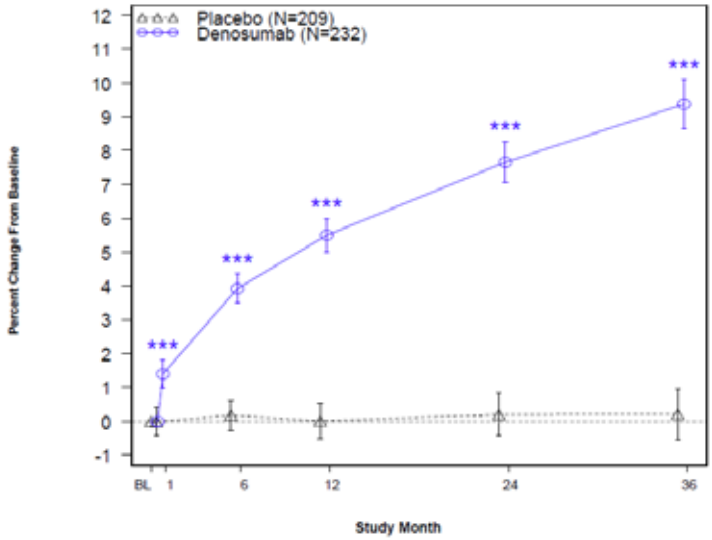


Figure 8 - Total hip BMD percentage change from baseline by visit (Study 20030216)

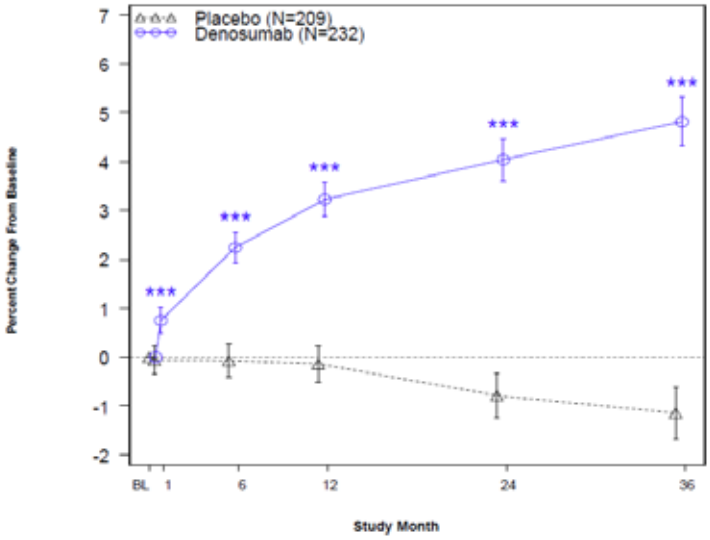
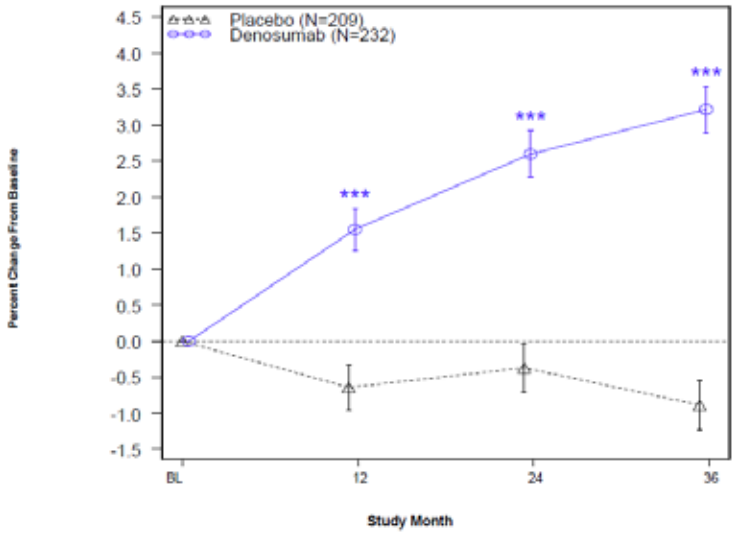


Figure 9 - Total body BMD percentage change from baseline by visit (Study 20030216)



In total, 103 patients were enrolled in the bone biopsy substudy, where samples of iliac crest bone were to be collected for quantitative histomorphometry. A total of 68 bone biopsies were obtained at Month 24 from 37 patients receiving placebo and 31 receiving denosumab, and at Month 36 from 25 patients receiving placebo and 22 receiving denosumab. Of these, 23 patients (17 receiving placebo, 6 receiving denosumab) had paired biopsies; that is, were sampled at both Months 24 and 36. In total, 103 patients were included in the bone biopsy substudy and these patients were broadly representative of the study population as a whole. Details of the histomorphometry conducted are included in this study's safety evaluation below.

The 209 patients enrolled in the spine and hip QCT substudy were also similar to the overall study population in terms of disposition, demographics and baseline disease characteristics. Similar results were achieved, with an increase in BMD in the denosumab group compared to placebo that achieved statistical significance ($p < 0.0001$) for the lumbar spine trabecular, total femur, total femoral neck and total trochanter. The 182 patients enrolled in the distal radius QCT substudy were representative of the study population as a whole, and at 36 months the denosumab group had significantly ($p = 0.0003$) increased BMD of cortical bone at the distal radius compared to placebo.

The bone marker substudy enrolled 160 patients. In addition to sharing common disposition, demographics and disease characteristics with the study population as a whole, they also had representative baseline serum calcium phosphorus, renal function, and the markers of bone turnover CTX1 and tartrate resistant acid phosphatase 5b (TRAP5b). In the case of both markers, the denosumab group experienced a rapid, lasting and statistically significant ($p < 0.0001$) decrease-from-baseline at all measured time points compared to placebo.

Two validated instruments for measuring patient-reported outcomes were used, including both generic (European Quality of Life, Five Dimensions) and disease-specific (Osteoporosis Assessment Questionnaire, Short Version). No statistically significant differences between the denosumab and placebo treatment groups were demonstrated.

Pivotal Trials in Treatment of Bone Loss in Hormonal Ablation

Two pivotal Phase III studies examined the use of denosumab in the treatment of bone loss in the context of hormonal ablation therapy. Two groups of patients were studied: women with non-metastatic breast cancer receiving aromatase inhibitor therapy, and men with non-metastatic prostate cancer receiving androgen deprivation therapy. These populations were

targeted due to increased frequency of bone loss as complications of hormonal therapy.[47,48] The pathophysiology for bone loss in this group is thought to be similar to that of osteoporosis, namely the relative or absolute lack of oestrogen and its attendant effect on skeletal integrity.

Study 20040135

Study Design and Patient Characteristics

This was a Phase III multicentre, randomized double-blind, placebo-controlled trial of the efficacy and safety of denosumab in treating bone loss in women with non-metastatic breast cancer with low bone mass who were receiving aromatase inhibitor therapy. Patients were randomized 1:1 in a double-blinded fashion to receive either placebo SC or denosumab 60 mg SC every six months for 18 months. The on-treatment phase therefore included four doses (Months 0, 6, 12, and 18) with follow-up to Month 24. Similar to the previous pivotal trial, all patients received at least 1 g of daily calcium and at least 400 IU of daily vitamin D supplementation as standard-of-care for bone loss. Randomization was stratified by months of aromatase inhibitor therapy, as up to six months or greater than six months. The duration of the trial was from October 2004 to May 2007. The study was conducted in compliance with GCP guidelines.

All enrolled patients had a lateral spine, femoral neck, total body and radius DEXA at screening, 12 months and at 24 months for any patients who discontinued treatment before this point. DEXA of the spine, femoral neck and total hip was also repeated on Day 30, and at 3 and 6 months. Lateral x-rays of the thoracolumbar spine were taken at screening and at 24 months (or exit).

An enrolment of 208 patients was planned, with 104 in each treatment arm. Inclusion criteria were women at least 18 years of age with histologically- or cytologically-confirmed early-stage, oestrogen-receptor-positive adenocarcinoma of the breast. Patients were required to be high-functioning (Eastern Cooperative Oncology Group [ECOG] class 0 or 1) and free of distant metastases.[49] All had completed their treatment pathways and were receiving an aromatase inhibitor. Exclusion criteria were similar to the other pivotal trials (no recent bisphosphonates or other agents known to affect bone metabolism, no fracture after the age of 25, lumbar spine, total hip or femoral neck BMD T-scores greater than minus 1.0 or less than minus 2.5) but also excluded patients with recurrent disease and those receiving anti-neoplastic agents.

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[47] Shapiro C, Manula J, Leboff M. Ovarian failure after adjuvant chemotherapy is associated with rapid bone loss in women with early stage breast cancer.J Clin Oncol 2001; 19: 3306-3311.

[48] Daniell HW. Osteoporosis after orchidectomy for prostate cancer. J Urol 1997; 337: 670-676.

[49] ECOG Performance Status. The Eastern Cooperative Oncology Group (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 self-care but unable to carry out any work activities. Up and about more than 50% of waking hours

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

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

5 - Dead

A total of 252 patients were enrolled, of whom 127 were randomized to receive denosumab and 125 placebo. Mean (±SD) age was 59.5 ± 9.3 years. The great majority (93%) were white or Caucasian. The two treatment groups were well-matched for baseline demographics, BMD T-scores, and disease characteristics. Of the 252 patients, 249 subjects (125 denosumab, 124 placebo) received at least one dose of the investigational product.

On-study protocol deviations were more common in this pivotal trial, but were similar in each group (21% in the placebo group, 17% for denosumab). Administrative errors in both groups (13 patients for placebo, 11 for denosumab) may account for the greater number of on-study protocol deviations in this trial. Another common cause of protocol deviation on-study was the taking of exclusionary medication, usually bisphosphonates (5% for the placebo group, 4% for denosumab).

There were no significant differences in patient disposition between the two treatment groups. 21 patients (17%) discontinued study treatment from the denosumab arm, compared to 26 patients (21%) receiving placebo. The reasons for withdrawal were well balanced between the two groups. The most common reason overall was withdrawal of consent (9% denosumab, 7% placebo). Withdrawals due to adverse events were uncommon (2 patients, both receiving placebo) and only 3 patients (all taking placebo) were lost to follow-up.

Exceeding the planned sample size of 208 patients provided a power of at least 95% to detect a difference of two percentage points in lumbar spine BMD at twelve months ($\alpha = 0.05$), which as mentioned above has been advanced as a clinically meaningful endpoint in comparable studies. The primary efficacy analysis was performed on the intention-to-treat population, with the per-protocol population used to provide additional sensitivity analyses.

Primary Efficacy Outcomes

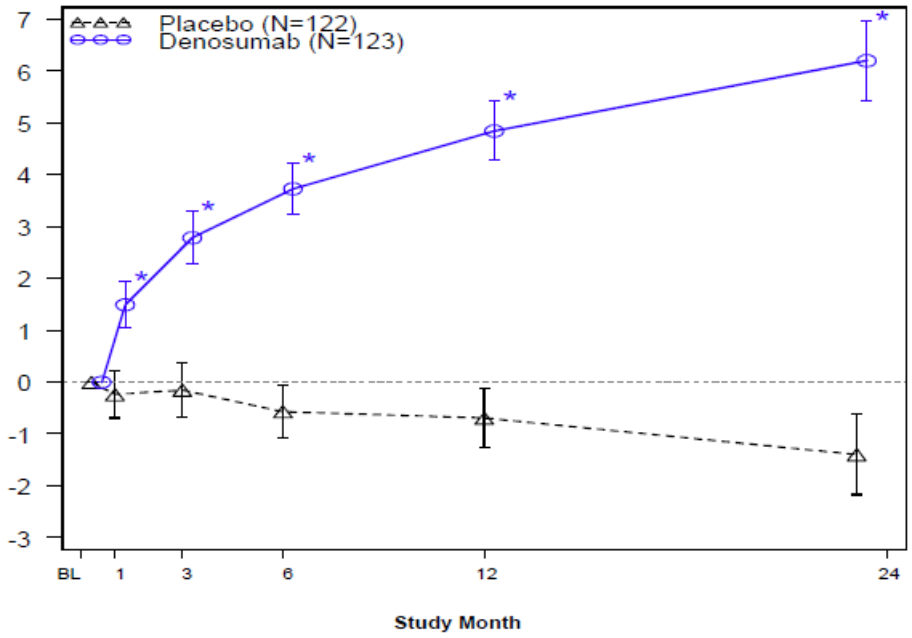
The primary efficacy measure was the percentage change in lumbar spine BMD from baseline to Month 12. This outcome was met to the point of statistical significance ($p <$ 0.0001), with a mean percentage change from baseline of 4.8% for denosumab (95% CI of 4.3% to 5.4%) compared to minus 0.7% for placebo (95% CI of minus 1.3% to minus 0.1%). This effect was robust across a number of sensitivity analyses, including the per-protocol population.

Secondary Efficacy Outcomes

Secondary efficacy outcomes included percentage change in lumbar spine BMD at Month 6, and in total hip and femoral neck BMD at Months 6 and 12.

The change in lumbar spine BMD was statistically significant ($p < 0.0001$) in the denosumab group compared to placebo at all time points from Month 3 onwards (Figure 10). At Month 6, the mean change in the denosumab group was 3.7% (95% CI of 3.2% to 4.2%) compared to -0.6% (95% CI of minus 1.1% to -0.1%).

Figure 10 - Percentage change from baseline in lumbar spine BMD, least-squares means method (Study 20040135)



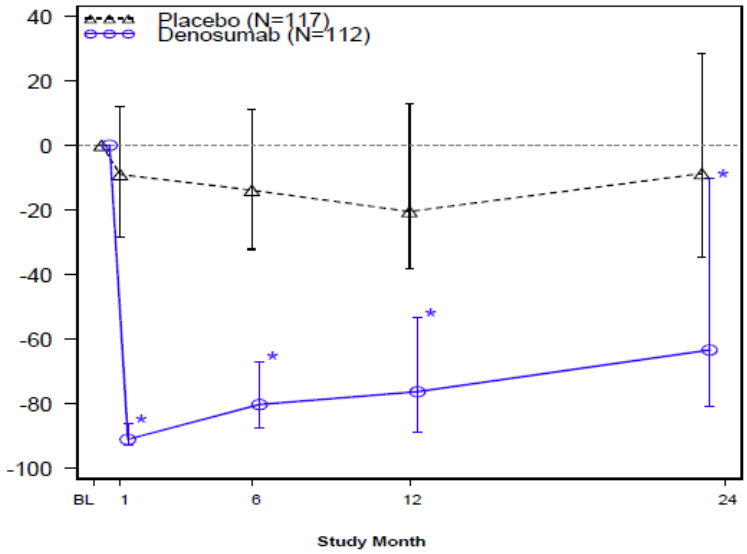
Denosumab significantly ($p < 0.0001$) increased total hip BMD at Months 6 and 12 in all sensitivity analyses. At Month 6 the difference was 2.3% (95% CI of 1.9% to 2.8%) for denosumab and -0.4% (95% CI of -0.8% to 0.1%) for placebo. At Month 12 the difference was more pronounced at 3.1% (95% CI of 2.6% to 3.5%) for denosumab and -0.7% (95% CI of minus 1.1% to -0.2%) for placebo. Differences between the groups were statistically significant ($p < 0.0001$) from Month 3. Similarly for changes in BMD at the femoral neck, denosumab significantly ($p < 0.0001$) increased BMD from Month 6. By Month 12, the mean change for the denosumab group was 1.9% (95% CI of 1.1% to 2.6%) compared to -0.6% (95% CI of minus 1.4% to 0.2%) for placebo.

As exploratory endpoints, change in distal radius, total body and trochanter BMDs were considered. At Month 24, denosumab significantly ($p < 0.0001$) increased BMD at the distal radius (2.1% compared to minus 3.9% for placebo), total body (2.6% compared to minus 1.6% for placebo) and trochanter (5.4% compared to -0.5% for placebo).

Bone turnover markers were explored, as they were for the previous pivotal trials. Instead of TRAP5b, procollagen type I N-terminal peptide (P1NP) was used as a measure of bone formation. Consistent with the experience of the previous pivotal trials, sCTX1 exhibited a rapid, sustained and significant ($p < 0.0001$) decrease for the denosumab group compared to placebo (Figure 11). The findings with P1NP were similarly significant ($p < 0.0001$) but less rapid, being most pronounced from Month 6.

No vertebral fractures were reported in either group during the trial. Nonvertebral, atraumatic and non-pathologic fractures were confirmed in 8 patients (6%) in each treatment group.

Figure 11 - Percentage change in sCTX1 from baseline by visit (Study 20040135)



Study 20040138

Study Design and Patient Characteristics

This was a Phase III international, multicentre, randomized double-blind, placebo-controlled trial of the efficacy and safety of denosumab in treating bone loss in men with low bone mass and non-metastatic prostate cancer treated with hormone deprivation therapy. Patients were randomized 1:1 in a double-blinded fashion to receive either placebo SC or denosumab 60 mg SC every six months for 36 months. The on-treatment phase therefore included six doses (Months 0, 6, 12, 18, 24 and 30) with follow-up to Month 36. All patients received at least 1 g of daily calcium and at least 400 IU of daily vitamin D supplementation as standard-of-care for bone loss. Randomization was stratified by months of androgen deprivation therapy (either from orchidectomy or pharmacologically) as up to six months or greater than six months. Randomization was also stratified by age at study entry, as less than or at least 70 years. The duration of the trial was from August 2004 to May 2008. The study was conducted in compliance with GCP guidelines.

All enrolled patients had a lateral spine, femoral neck, total hip, total body and radius DEXA at screening, 12 months, 24 months and at 36 months for any patients who discontinued treatment before this point. DEXA of the spine, femoral neck and total hip was also repeated on Day 30, and at 3 and 6 months. Lateral x-rays of the thoracolumbar spine were taken at screening and at 24 months (or exit). A bone scan was performed a 36 months (or termination).

An enrolment of 1226 patients was planned, with 613 in each treatment arm. Inclusion criteria were men with histologically-confirmed non-metastatic adenocarcinoma of the prostate. Men under the age of 70 were also required to have a history of osteoporotic fracture or a BMD T-score at the lumbar spine, total hip or femoral neck of less than minus 1.0. Patients were required to be high functioning (ECOG class 0, 1 or 2). All had stable disease, adequate organ function, and had either undergone orchidectomy or were receiving androgen deprivation therapy with a plan to continue doing so for at least twelve months. Exclusion criteria were similar to the other pivotal trials (no recent bisphosphonates or other agents known to affect bone metabolism, distant metastases, no systemic antineoplastic therapy other than androgen deprivation therapy, and no BMD T-score less than minus 4.0 at the lumbar spine, total hip or femoral neck).

A total of 1468 patients were enrolled, of whom 734 were randomized to receive denosumab and 734 to receive placebo. Mean (±SD) age was 75.4 ± 7.1 years. The majority (83%) were white or Caucasian. The two treatment groups were well-matched for baseline demographics, BMD T-scores, previous fracture history and disease characteristics. These characteristics did not differ markedly between the randomization strata. Of the 1468 patients, 1456 subjects (731 denosumab, 725 placebo) received at least one dose of the investigational product.

On-study protocol deviations were slightly more common for the denosumab group (19%) than for those receiving placebo (17%). The most common cause of on-study protocol deviation was missing data (9% for denosumab, 7% for placebo) followed by administrative errors such as improper storage of the investigational product (7% for denosumab, 8% for placebo).

There were no significant differences in patient disposition between the two treatment groups. 267 patients (36%) discontinued study treatment from the denosumab arm, compared to 289 patients (39%) receiving placebo. The reasons for withdrawal were well balanced between the two groups. The most common reason overall was withdrawal of consent (17.3% denosumab, 19.5% placebo). Withdrawals due to adverse events were more common in the denosumab group (29 patients, 4.0%) than for placebo (22 patients, 3.1%). 17 patients receiving denosumab and 21 receiving placebo were lost to follow-up (an overall rate of 2.6%, considered reasonable in a study of this design and duration).

Primary Efficacy Outcomes

The primary efficacy endpoint was the percentage change in lumbar spine BMD from baseline at 24 months (Figure 12). Denosumab significantly ($p < 0.0001$) increased BMD at the lumbar spine at Month 24, compared to placebo. Using a least-squares method, the mean percent changes from baseline to Month 24 were 5.6% in the denosumab group and minus 1.0% in the placebo group. This was a robust effect across strata and using the per-protocol and intention-to-treat populations. This effect was maintained and remained statistically significant ($p < 0.0001$) at 36 months, where the least-squares mean percent change was 6.8% for denosumab and minus 1.2% for placebo.

Secondary Efficacy Outcomes

Denosumab significantly ($p < 0.0001$) increased BMD at the total hip (Figure 13) and femoral neck (Figure 14) at Month 24. These increases remained significant through Months 30 and 36. For the total hip, BMD at Month 36 was increased by an average of 3.2% for those treated with denosumab compared to minus 2.6% for those treated with placebo ($p < 0.0001$). For the femoral neck, BMD at Month 36 was increased by an average of 3.0% for the denosumab group compared to minus 1.8% for placebo ($p < 0.0001$).

Figure 12 - Lumbar spine BMD percentage change from baseline by visit (Study 20040138)

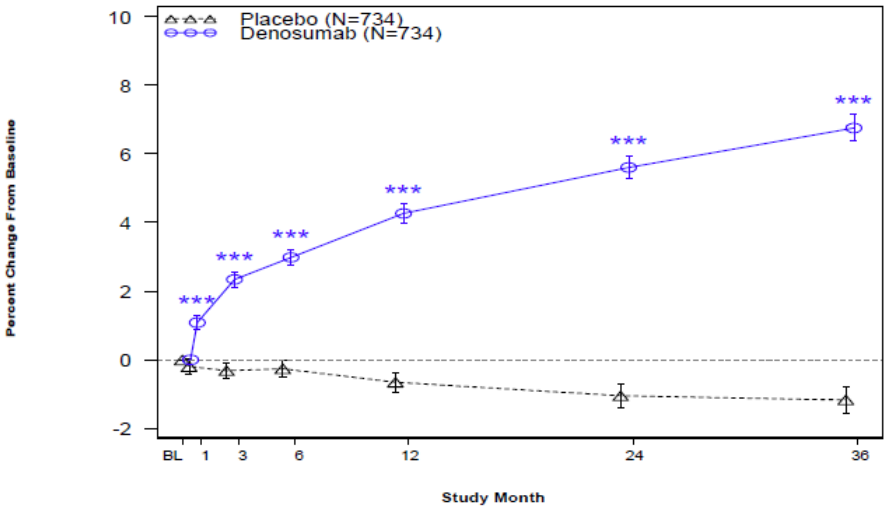
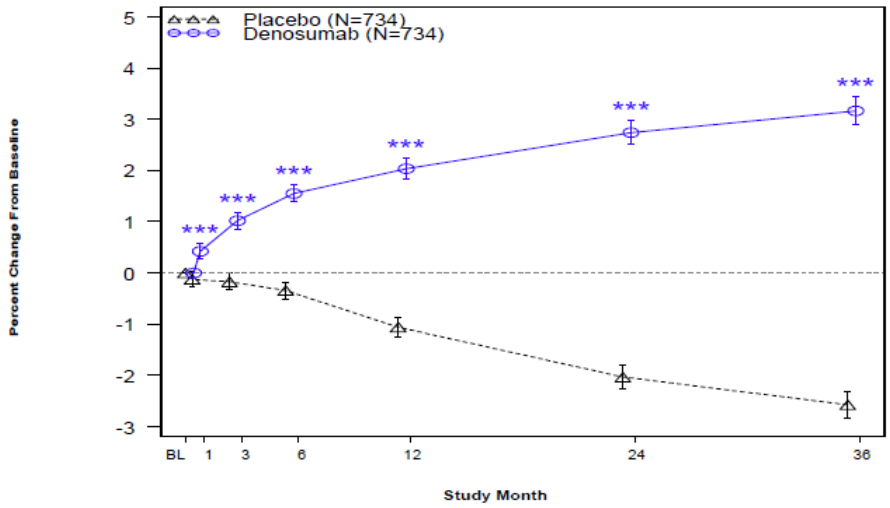


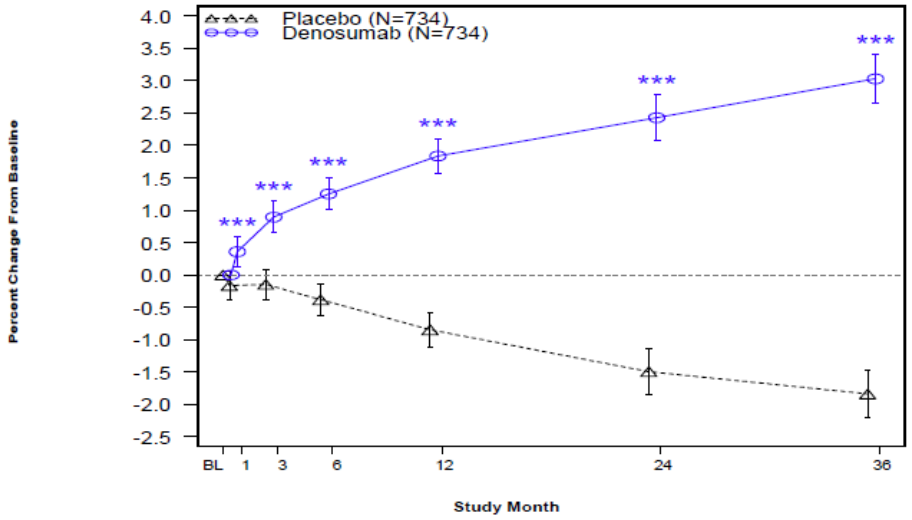
Figure 13 - Total hip BMD percentage change from baseline by visit (Study 20040138)



Treatment with denosumab reduced the incidence of new vertebral fractures over the 36 months of observation by 62% (p = 0.0125). At this time point, 10/679 patients (1.5%) treated with denosumab had recorded a new vertebral fracture, compared to 26/673 patients (3.9%) treated with placebo. Sensitivity analyses across strata and using the per-protocol or intention-to-treat populations confirmed a robust effect.

At Months 24 and 36, the incidence of any fracture was lower in the denosumab group (4.4% and 5.2%) compared to placebo (6.1% and 7.2%), but this did not achieve statistical significance (p = 0.796 and p = 0.105 for 24- and 36-month comparisons respectively). Time to first clinical fracture did not significantly differ between the two groups.

Figure 14 - Femoral neck BMD percentage change from baseline by visit (Study 20040138)



Assays of CTX1, TRAP5b and P1NP were undertaken as exploratory endpoints and surrogate markers of efficacy as indices of bone turnover. All three showed the early and sustained decreases noted in previous pivotal trials, achieving statistical significance from the first post-dose assessment.

Two validated quality-of-life questionnaires were undertaken to assess patient-reported outcomes, namely the Expanded Prostate Cancer Index Composite (EPIC) and European Quality-of-life Five Dimensional (EQ-5D) tools. Both found trends-to-improvement with denosumab which did not achieve statistical significance and were not clinically meaningful.

Longer-term Efficacy Studies in Post-Menopausal Osteoporosis

Study 20040132

Study Design and Patient Characteristics

Study 20040132 was a non-pivotal Phase III study of the efficacy and safety of denosumab in the prevention of lumbar spine bone loss in post-menopausal women with low bone mass (as evidenced by a baseline BMD T-score of between minus 1.0 and minus 2.5). The trial reported on safety and efficacy at the end of the 24-month on-treatment period.

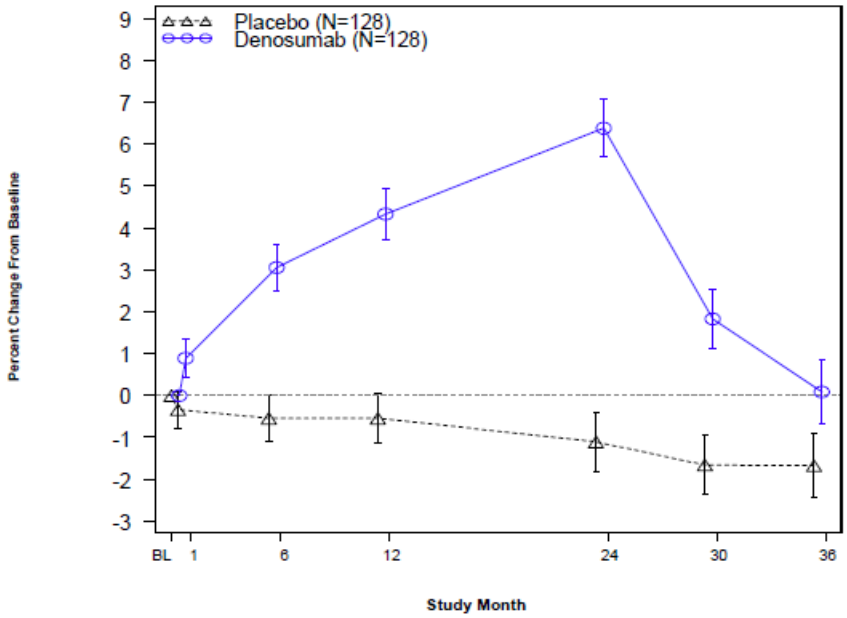
The report analysed here comprises an interim analysis of efficacy and safety during an optional, off-treatment 24-month extension phase; this report includes the first 12 months of data from the extension study. This study shared the same design, efficacy and safety measures as those outlined below. Being an off-treatment period, no denosumab was administered during the extension phase. Visits were made at Months 24, 27, 30 and 36 (with two further visits at 42 and 48 months to be presented in a future report). DEXA of the spine, hip, and distal radius was undertaken at Months 24, 30 and 36; DEXA of the total body was undertaken at Months 24 and 36 only.

A total of 128/142 patients (77%) randomized to receive denosumab and 128/144 patients (77%) randomized to placebo elected to enrol in the off-treatment extension phase. At the time of this report, 12 months into the off-treatment period, 116/128 patients (91%) who had received denosumab and 118/128 patients (92%) who had received placebo were ongoing. The demographics of these patients were not significantly different from the entry population of Study 20040132 overall.

Primary Efficacy Outcomes

For patients treated with denosumab, BMD at the lumbar spine had increased during the 24-month period of active treatment (by a mean of 6.4%). Within 12 months of cessation of treatment, BMD at the lumbar spine fell by a mean of 5.8% in patients previously treated with denosumab (Figure 15). For the patients in this group, therefore, the total BMD change over 24 months of denosumab treatment and 12 months without it was 0.1% at the lumbar spine. By comparison, the mean change for patients treated with placebo for 24 months and off-treatment for 12 months was a 1.7% decrease in lumbar spine BMD. The difference was statistically significant ($p \leq 0.001$) although the clinical meaning of such a difference is not known.

Figure 15 - Lumbar spine BMD by DEXA as percent change from baseline by visit (Study 20040132, extension phase)



Secondary Efficacy Outcomes

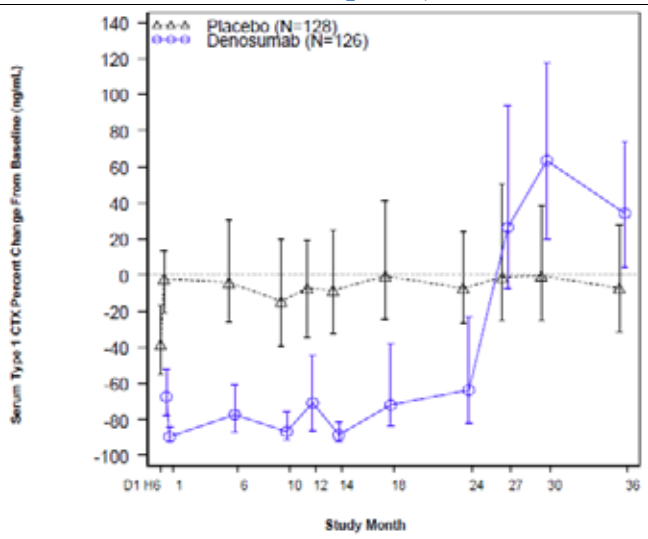
A trend of return-to-baseline was seen in BMD at all sites for denosumab-treated patients, including the total hip, femoral neck, distal radius and total body. At all sites this corresponded with a continued steady decrease in mean BMD for patients who had received placebo during the on-treatment period. The differences were statistically significant ($p \leq 0.001$) at the total hip and distal radius. These effects were robust including or excluding eight patients who had received other treatments known to effect bone metabolism during the off-treatment period.

Interestingly, the assayed markers of bone turnover did not return to pre-treatment levels, but increased during the presented 12 months of the off-treatment period. The effect was noted for CTX1 (Figure 16), TRAP5b and P1NP and appeared significant. For example, median CTX1 six months after ceasing therapy was 63% higher than it had been pre-treatment.

If it is accepted that these markers are reasonable indices of bone turnover, the evaluator was concerned that withdrawal of denosumab therapy may be associated with a rebound or "catch-up" phenomenon. It is acknowledged that this is not yet reflected in a net decrease in BMD after withdrawal, but the slope of BMD falls at all sites on ceasing denosumab treatment does appear rapid and may correspond with rates of bone loss faster than the

natural history of osteoporosis. Whether this translates into clinically meaningful outcomes such as increased fracture rates on withdrawal remains to be seen. In the 12 months of off-treatment period reported here, only two confirmed clinical fractures had occurred in both groups (although in total six denosumab patients and three placebo patients had adverse events of "fracture" recorded).

Figure 16 - Median sCTX1 percent change from baseline by visit (Study 20040132, extension phase)



Study 20050233

Study Design and Patient Characteristics

This trial was a Phase III open-label, single-arm extension study of the long-term safety of denosumab in post-menopausal women with low bone mass. It had no primary efficacy outcomes, being chiefly a study of long-term safety, but did report secondary efficacy measures including changes from baseline in lumbar spine, hip, femoral neck, trochanter and distal radius. In addition, the bone turnover markers CTX1 and bone-specific alkaline phosphatase (BSAP) were presented as further secondary measures of efficacy. The trial was conducted in accordance with GCP principles, began in May 2006, and is ongoing although only the first twelve months' data is presented here.

The study was designed as an open-label extension to an earlier phase II dose-ranging study, Study 20010223 reviewed above. As such, it shared a similar design and drew its population from the same pool of patients, namely post-menopausal women who had completed Study 20010223, were ambulatory and in good health, no more than 80 years old, and had low bone mass (BMD T-scores between minus 1.8 and minus 4.0 in the lumbar spine, or between minus 1.8 and minus 3.5 in the total hip or femoral neck).

Patients in this trial were assigned to cohorts depending on their earlier exposures in Study 20010223. In total, 200/262 patients (76.3%) who were eligible chose to enrol in the study. The continuous-treatment cohort comprised 124 patients who had received escalating doses from 6 mg to 100 mg denosumab for two years, then 60 mg denosumab six-monthly for two years. The placebo cohort included 23 patients who had received placebo for four years. The retreatment cohort comprised 14 patients who received denosumab 30 mg three-monthly for two years, placebo for one year, then denosumab 60 mg six-monthly for one year. The off-

treatment cohort included 17 patients who had received denosumab 210 mg for two years, then placebo for two years. The alendronate cohort comprised 22 patients who had received alendronate 70 mg weekly for two years, and no alendronate for two years. All patients proceeding into this extension study received denosumab 60 mg six-monthly, so for two cohorts, the alendronate and placebo groups, or 45 patients, this study represented the first exposure to denosumab.

There were no significant differences in baseline characteristics or disposition by cohort. Fourteen patients (7%) withdrew from the study during the 12 months of data presented here, most commonly as a result of withdrawn consent (6 patients) and adverse events (5 patients).

Secondary Efficacy Outcomes

For patients in the continuous treatment cohort, the additional 12 months of denosumab treatment resulted in further gains in BMD. The least-squares mean change in BMD was a further 1.4% at the lumbar spine, 0.9% at the total hip, 0.6% at the femoral neck, 1.4% at the trochanter and 0.8% at the distal radius.

For those patients in the placebo cohort, the first 12 months of their denosumab treatment resulted in significant gains in BMD, including 5.9% at the lumbar spine, 3.1% at the total hip, 3.8% at the femoral neck, 4.2% at the trochanter, and 1.5% at the distal radius.

Changes in mean BMD were mixed in the other cohorts, but showed a (non-statistically significant) trend to improvement. The lack of statistical significance is most likely the result of small cohort sizes.

Reductions in the biochemical markers of bone resorption and formation were sustained over the 12 months of treatment. For the continuous treatment cohort, median reductions in CTX1 ranged from 3.3 to 64.3% at twelve months. Median reductions in BSAP ranged from 29.1% to 49.6%. For patients in the retreatment, off-treatment, placebo and alendronate cohorts, reductions in these markers tended to be greatest at the Month 1 measurement.

Only one fracture was recorded during the study window, namely an osteoporotic rib fracture reported in one patient (from the continuous treatment cohort).

Study 20060289

Study Design and Patient Characteristics

This study is planned as a large, ongoing international, multi-centre, open-label single-arm extension study enrolling patients who completed Study 20030216, one of the pivotal studies analysed above. It will be an 84 month trial where all patients will receive 60 mg denosumab at Months 0, 6, 12 and 18, and all patients will be followed until Month 84. As of the data cut-off date (May 2008), 4307 of the planned 4900-5600 patients had been enrolled. Inclusion and exclusion criteria are as for Study 20030216, namely ambulatory postmenopausal women with osteoporosis who had completed the 36-month visit of Study 20030216.

The study report is in interim synopsis form only and is incomplete, giving as its only efficacy measure the Day 10 adjusted calcium.

Primary Efficacy Outcomes

The primary endpoint is safety monitoring and no efficacy data is presented in the interim synopsis.

Secondary Efficacy Outcomes

Secondary efficacy measures when this trial is completed will include change in BMD by DEXA at the lumbar spine, total hip and distal radius, the incidence of vertebral fractures at Month 24, non-vertebral fractures at Months 12 and 24, five-year values of bone turnover markers, and Day 10 adjusted calcium. For patients who received denosumab during the early 20030216 study, bone histomorphometry based on micro-computerised tomography of transiliac biopsy samples will be undertaken.

The only data presented in this interim synopsis is Day 10 calcium data. This time point has been chosen because preclinical studies suggested a post-dose nadir of calcium around ten days. In the 2032 patients treated *de novo*, the median corrected calcium levels were 9.20 mg/dL. In the 2163 patients treated long-term, the median corrected calcium was 9.40 mg/dL. This represented a change from baseline of minus 3% in *de novo* patients and minus 2% in long-term patients.

Non-Pivotal Trials in Post-Menopausal Osteoporosis

Study 20040132

Study Design and Patient Characteristics

This was a Phase III multicentre, randomized double-blind, two-period parallel-group placebo-controlled trial of the efficacy and safety of denosumab in preventing lumbar spine bone loss in postmenopausal women with a lumbar spine BMD T-score of between minus 1.0 and minus 2.5. Of note, this is suggestive (but not identical to) the accepted WHO definition of "osteopenia" and "low bone mass" rather than "osteoporosis".[9] Patients were randomized 1:1 in a double-blinded fashion to receive either placebo SC or denosumab 60 mg SC every six months for 18 months. The on-treatment phase therefore included four doses (Months 0, 6, 12, and 18) with follow-up to Month 24. As was the case in the previous pivotal trial, all patients received at least 1 g of daily calcium and at least 400 IU of daily vitamin D supplementation. Randomization was stratified by years of menopause, as up to five years or greater than five years. The duration of the trial was from August 2004 to February 2007. The study was conducted in compliance with GCP guidelines.

All enrolled patients had a lateral spine X-ray and DEXA at screening and at 24 months for any patients who discontinued treatment before this point. On Day 1, DEXA of the hip, distal third of radius and total body was also undertaken. This was repeated at 12 and 24 months.

An enrolment of 300 patients was planned, with 150 in each treatment arm. Inclusion criteria were postmenopausal status (either absent menses 12 months, or confirmed by high serum follicle stimulating hormone and low serum oestradiol), aged up to 90 years, ambulatory and in good health, and a bone mineral density (BMD) T-score between minus 2.5 and minus 1.0 at the lumbar spine. Exclusion criteria were as for the previous pivotal trial, with the additional requirement for no fractures after the age of 25 years.

A total of 332 patients were enrolled, of whom 166 received denosumab and 166 received placebo. Mean (±SD) age was 59.4 ± 7.5 years. The majority (83%) were white or Caucasian. The two treatment groups were well-matched for baseline demographics and BMD T-scores. Of the 332 patients, 329 subjects (164 denosumab, 165 placebo) received at least one dose of the investigational product.

There were no significant differences in patient disposition between the two treatment groups; 24 patients (14%) discontinued study treatment from the denosumab arm, compared to 22 patients (13%) receiving placebo. The reasons for withdrawal were moderately balanced between the two groups. The most common reason overall was withdrawal of consent (6% denosumab, 9% placebo). Withdrawals due to adverse events were uncommon

in both groups (1% each); 12 patients (4%) were lost to follow-up. On-study protocol deviations were similar in each group (8% in the placebo group, 7% for denosumab). The more common causes for the denosumab group were the taking of exclusionary medications (7 patients), whereas administrative causes were more common in the placebo group (7 patients).

The planned sample size of 300 patients was met, providing a power of 90% to detect a difference in lumbar spine BMD of two percentage points between denosumab and placebo ($\alpha = 0.025$). Similar measures have been advanced as clinically meaningful in comparable clinical trials comparing active and placebo in osteoporosis.[50] The primary efficacy subset comprised the intention-to-treat population, with the per-protocol population used as additional sensitivity analyses for some endpoints. The full analysis subset, including all randomized patients, was used for the time-to-first-clinical-fracture endpoint.

Primacy Efficacy Outcomes

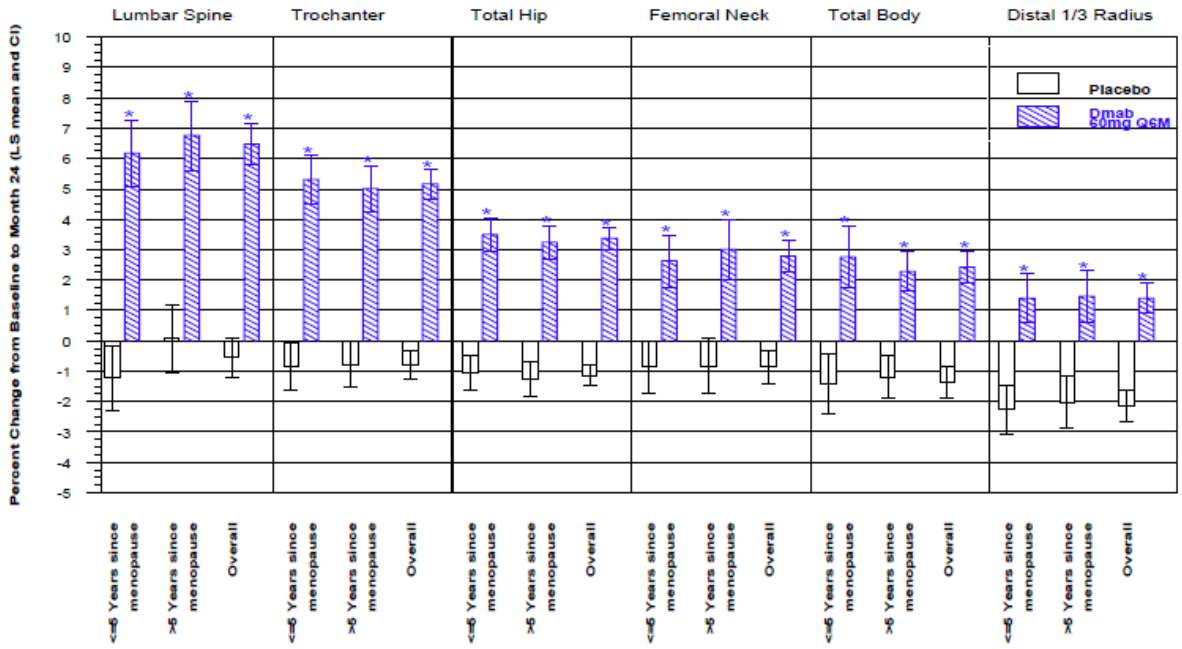
The primary efficacy measure was lumbar spine BMD as assessed by DEXA at 24 months. Denosumab significantly increased BMD compared to placebo for both early and late menopausal women. The effect was statistically significant ($p < 0.0001$) and robust across a number of sensitivity analyses. Using a least-squares technique, the mean change in BMD from baseline to Month 24 was 6.2% for the denosumab group and minus 1.2% for placebo ($p < 0.0001$). Similar magnitudes of change were seen across both strata and overall, at all time points, and all were significant.

Secondary Efficacy Outcomes

Secondary efficacy measures included changes in BMD at a number of sites, including the total hip, femoral neck, trochanter, distal radius and total body. Denosumab significantly increased BMD compared to placebo at 24 months (Figure 17), at all sites and across both strata and overall ($p < 0.001$). The difference was greatest at the trochanter (6.0%, 95% CI of 5.3% to 6.6%), followed by the total hip (4.5%, 95% CI of 4.0% to 5.0%) and total body (3.8%, 95% CI of 3.1% to 4.5%).

[50] Johnston CC, Bjarnason NH, Cohen FJ. Long-term effects of raloxifene on bone mineral density, bone turnover, and serum lipid levels in early postmenopausal women. Arch Intern Med 2000; 160: 3444-3450.

Figure 17 - BMD by DEXA at discrete sites as percent change from baseline at Month 24 (Study 20040132)



As an additional efficacy measure, trabecular, cortical and total volumetric data from the distal radius was collected by an experimental quantitative computed tomography technique. Although all showed a trend to improvement in the denosumab group compared to placebo, statistical significance was not reached for any site or strata (p = 0.025 to 0.05).

A number of exploratory endpoints were also investigated, including the bone markers assayed in the previous pivotal trial (CTX1 and TRAP5b), fracture outcomes, and the effect of body weight and body mass index (BMI) on BMD.

Denosumab significantly ($p < 0.0001$) decreased serum concentrations of CTX1 compared to the placebo group, at each time point sampled. At 24 months the change was minus 63.0% (interquartile range minus 82.2% to minus 22.5%) for denosumab, compared to minus 5.9% for placebo (interquartile range minus 5.4% to +27.1%). This reflected the experience of the previous pivotal study. Similar results were obtained for TRAP5b.

Clinical and confirmed fractures were considered exploratory endpoints in the design of this trial, and were reported in 2 patients (1%) in the denosumab group and 7 patients (4%) receiving placebo. All were non-vertebral.

Under linear regression analysis, no significant linear correlations with BMD were noted for either weight or BMI.

Study 20050141

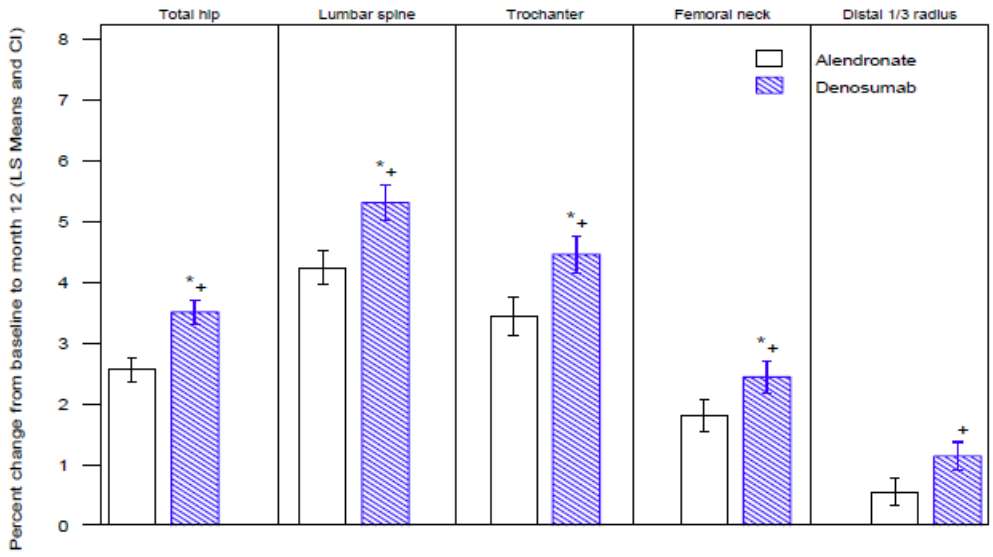
This was an international, multi-centre, randomized, double-blind, active controlled, double-dummy parallel-group study comparing the efficacy of denosumab 60 mg six-monthly with that of a widely-used standard-dose bisphosphonate, alendronate 70 mg weekly. Postmenopausal women with BMD T-scores of at least minus 2.0 at the lumbar spine or total hip were randomized in a blinded 1:1 fashion to receive either denosumab and placebo, or placebo and alendronate, for twelve months. Supplemental calcium (at least 500 mg daily) and vitamin D (at least 400 IU daily) were to be continued during the trial. The trial was

conducted between April 2006 and December 2007 and ran in accordance with GCP procedures.

A total of 1179 patients received at least one dose of the investigational product, including 593 patients who received denosumab and 586 who received alendronate. The study was completed by 94% of patients in the denosumab group and 93% of patients receiving alendronate.

All primary and secondary efficacy endpoints were met with statistical significance ($p < 0.0001$). At all sites, a significant increase in BMD by DEXA was seen at the end of the 12 treatment months (Figure 18). Inferences of treatment effect were made after denosumab was shown to be non-inferior to alendronate with respect to mean percent change in total hip BMD at twelve months ($\alpha = 0.025$). The non-inferiority margins used were derived from three published trials of alendronate treatment of postmenopausal women where BMD was measured for at least one year. These were calculated as 50% of the lower bounds of the 95% confidence intervals for those trials' treatment differences (that is, alendronate - placebo). This approach seems reasonable but it was noted that only one of these trials used to derive non-inferiority used alendronate dosed as 70 mg weekly (in 327 patients), as it was in this trial, Study 20050141. As the study was sufficiently powered to demonstrate this non-inferiority, superiority testing was performed and superiority for denosumab over alendronate was demonstrated for the lumbar spine, femoral neck, total hip, trochanter and distal radius ($p < 0.0001$). Patients receiving denosumab also had significantly greater decreases in serum concentrations of CTX1 at Months 1, 3, 6 and 9.

Figure 18 - BMD by DEXA as change from baseline at 12 months (Study 20050141)



Fractures were reported in 18 patients (3%) receiving denosumab and 13 patients (2%) receiving alendronate; statistical significance was not reported.

Study 20050179

This was a Phase II multicentre, randomized, double-blind, double-dummy, placebo-controlled pilot study designed to estimate the effect of treatment with denosumab in postmenopausal women with low bone mass using the emerging technology of *in vivo* micro-computed tomography. A total of 247 women with a lumbar spine or total hip BMD T-score of between minus 2.0 and minus 3.0 were randomized in a blinded 1:1:1 fashion to receive denosumab (83 patients), alendronate (82 patients) or placebo (82 patients). Treatment was

continued for 12 months. The trial was conducted between May 2006 and April 2008 and was conducted along GCP principles.

A number of derived parameters were available for analysis from the use of quantitative CT scanning using high-resolution devices, in addition to the usual DEXA BMD evaluations at sites including the distal radius, lumbar spine, femoral neck, trochanter and total hip. The quantitative CT methods at the distal radius (cortical thickness, QCT) correlated with DEXA findings of increased density under treatment with alendronate or denosumab but not placebo. At Month 12 at the distal radius, denosumab had increased mean cortical thickness by 1.1% (95% CI of 0.5 to 1.8) compared to 0.0% (95% CI of -0.6 to 0.7) for alendronate and minus 2.1% (95% CI of minus 2.7% to minus 1.4%) for placebo.

Denosumab treatment led to the expected decrease in median concentrations of the bone turnover markers CTX1, P1NP, BALP and TRAP5b.

Study 20050234

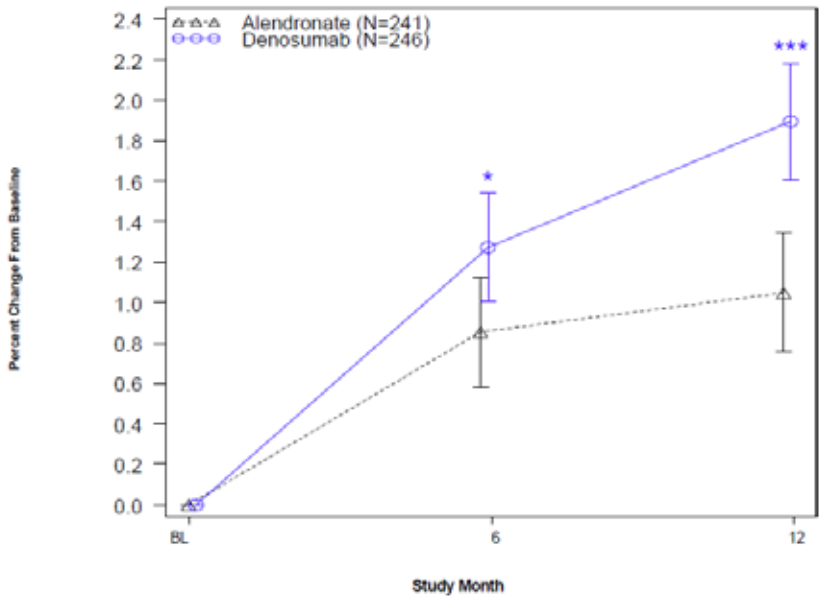
This was a Phase IIIb international, multicentre, randomized, double-blind, active-controlled double-dummy, parallel-group study of transitioning therapy from alendronate to denosumab in postmenopausal women with low bone mass. Overall, 504 women with lumbar spine or total hip BMD T-scores between minus 2.0 and minus 4.0 and who had been taking 70 mg alendronate weekly (or equivalent) for six months, were randomized 1:1 to receive either alendronate 70 mg weekly and placebo six-monthly (251 patients), or placebo weekly and denosumab 60 mg six-monthly (253 patients). The two groups were stratified according to duration of previous alendronate therapy (less than six months, six to twelve months, longer than twelve months). After a one-month run-in period, treatment was continued for 12 months. The trial was conducted between October 2006 and March 2008 in accordance with GCP principles.

The mean percent change from baseline in total hip BMD at Month 12 was 1.90% in the denosumab group and 1.05% in the group who continued to be treated with alendronate (Figure 19), or a difference of 0.85% (95% CI of 0.44% to 1.25%, $p < 0.0001$).

A study population greater than 470 patients provided greater than 90% power to demonstrate non-inferiority, according to a non-inferiority margin derived from comparable trials. After non-inferiority was demonstrated, superiority testing was significantly in favour of the denosumab group in changes in BMD at the total hip, lumbar spine, femoral neck, trochanter and distal radius ($p \leq 0.01$ at the 2-sided, 5% level).

Patients in the denosumab group also had a significantly greater decrease ($p \leq 0.01$) in sCTX1 from baseline at all time-points compared to those who had continued on alendronate therapy.

Figure 19 - Mean percentage change in BMD by DEXA at the total hip, Month 12 (Study 20050234)



Study 20060232

This was an interim report of a Phase IIIb, multicentre, randomized, cross-over open-label study of the adherence, preference and satisfaction of denosumab and alendronate in postmenopausal women with low bone mineral density. The study began in October 2007 and is ongoing; a total of 203 women with BMD T-scores between minus 2.0 and minus 4.0 had been enrolled by the time of data cut-off in May 2008. Of these, 103 women were randomized to receive 60 mg denosumab six-monthly for 12 months followed by 70 mg alendronate weekly for 12 months, and 100 were randomized to receive 70 mg alendronate weekly for 12 months followed by 60 mg denosumab six-monthly for 12 months.

No efficacy data were presented in the interim synopsis of this study.

Study 20060237

This was an interim report of a Phase IIIb, multicentre, randomized, open-label study to evaluate the safety of denosumab in a pre-filled syringe compared with denosumab in a vial. The study was designed as an extension to Study 20050141, analysed above, and shares with it its inclusion and exclusion criteria. The study began in May 2007 and was ongoing at the time of data cut-off in March 2008; the report therefore includes 6-month results. A total of 311 patients were enrolled from Study 20050141 and were randomized 1:1 to receive denosumab 60 mg from a vial (155 patients) or from a prefilled syringe (156 patients). The study was conducted according to GCP principles.

A total of 140/155 (90%) patients who had received denosumab using the vial and 146/156 (94%) patients who had received denosumab from a prefilled syringe had a baseline and at least one post-baseline antibody sample available for analysis. All patients tested negative to anti-denosumab antibodies at baseline, and remained so at Month 1 and Month 6; there was therefore no difference in immunogenicity between the two delivery systems.

Other Trials and Indications

Study 20040144

This was a Phase II, multicentre, randomized double-blind placebo-controlled study of the efficacy of denosumab in decreasing the progression of structural damage in patients with rheumatoid arthritis already receiving methotrexate. A secondary aim was to determine the safety and tolerability of an effective dose of denosumab for future studies in patients with rheumatoid arthritis. A total of 207 patients were enrolled and randomized in a 1:1:1 fashion to receive two six-monthly doses of placebo (78 patients), denosumab 60 mg (73 patients) or denosumab 180 mg (76 patients). An additional period of twelve months of non-treatment was observed for safety. The trial was conducted between August 2004 and April 2007 and ran in accordance with GCP guidelines.

The primary efficacy endpoint was the change from baseline at Month 6 in an MRI erosion score. A difference in MRI erosion score was found between the 180 mg denosumab group and the placebo group ($p = 0.018$); 12-month comparisons of radiographic data found significant differences between each of the denosumab groups and placebo.

BMD was measured at the lumbar spine, femoral neck, trochanter, total hip and hands via DEXA. The greatest change from baseline in lumbar spine BMD was seen in the 180 mg denosumab group (4.09%, $p < 0.001$). It was lower for the 60 mg denosumab group but still statistically significant (3.0%, $p < 0.001$).

Treatment with denosumab was associated with a reduction in markers of bone turnover, as had been seen in other studies. Denosumab treatment was also associated with a decrease in CTX2, a marker of cartilage turnover.

Study 20040113

This trial was a Phase II, multicentre, randomized, partially blinded, multiple dose, active-controlled parallel group study of the efficacy and safety of denosumab in the treatment of women with advanced metastatic breast cancer with bony metastases who had not already received intravenous bisphosphonate therapy. A total of 255 women were enrolled, of whom 212 were then randomized to receive either intravenous bisphosphonate (43 patients), 30 mg denosumab four- weekly (42 patients), 120 mg denosumab four-weekly (42 patients), 180 mg denosumab four- weekly (43 patients), 60 mg denosumab 12-weekly (42 patients) or 180 mg denosumab 12-weekly (43 patients). The study was conducted between September 2004 and June 2006.

The primary efficacy endpoint concerned urinary N-telopeptide, which was offered as a biochemical marker of bone resorption (and was used as such during the clinical development of the bisphosphonates). When adjusted for creatinine, the combined denosumab groups (-73%) and the bisphosphonate group (-78%) exhibited comparable suppression of urinary N-telopeptide. By Weeks 13 and 25, the incidence of skeletal-related events was similar in patients who had received denosumab (10% and 12% respectively) to those who had received bisphosphonates (14% and 16%).

Study 20040114

This study was a Phase II, multicentre, randomized, open-label, active-controlled, parallel-group, multidose study in patients with advanced cancer (solid tumours except lung, but including multiple myeloma) and bony metastases. To be eligible, patients needed a concentration of urinary N-telopeptide of at least 50 nM/mM during pre-study bisphosphonate therapy. In total, 111 patients were randomized to receive intravenous bisphosphonate (47 patients), denosumab 180 mg four-weekly (38 patients) or denosumab 180 mg 12-weekly (36 patients). The trial was conducted between December 2004 and January 2008 and complied with GCP practices.

The primary efficacy measure was urinary concentration of N-telopeptide when corrected for creatinine. The proportion of patients with less than 50 nM/mM at Week 13 was significantly greater ($p < 0.001$) in the combined denosumab groups (71%) compared to those receiving bisphosphonates (29%). The effect remained significant for both denosumab dose group, and was robust across subgroup analyses by cancer type and urinary N-telopeptide at screening, as well as in the per-protocol subset.

Study 20050134

This was a Phase II, multicentre, open-label, non-comparative, two-cohort proof-of-concept study for evaluating the efficacy and safety of denosumab 120 mg administered on Days 1, 8, 15, 29 and every subsequent 28th day in patients with relapsed or plateau-phase multiple myeloma. The trial commenced in February 2006 and is ongoing, having enrolled 53 patients with relapsed multiple myeloma and 43 with plateau-phase multiple myeloma at the time of data cut-off in August 2007.

The primary outcome measure was the rate of complete remission, partial remission or minimal response (as defined by serum M-protein assessments and confirmed with modified Bladé criteria).[51] None of the 53 patients with relapsed or plateau-phase multiple myeloma had a complete or partial remission, or even a minimal response.

Efficacy Conclusions

The three pivotal trials were of adequate design and addressed the indications being sought for denosumab in the sponsor's application. They were conducted in appropriate patient populations and generally employed acceptable and validated end-points (incidence of new fractures for fracture risk reduction, BMD by DEXA for treatment of bone loss).

The pivotal study 20030216 demonstrated a statistically significant reduction in its primary endpoint, the incidence of new vertebral fracture, for patients treated with denosumab at 12, 24 and 36 months. Kaplan-Meier estimates of incidences of nonvertebral and hip fractures at these time points, and the 36-month crude incidences of these fractures, were lower in the denosumab-treated group although this was not statistically significant.

The pivotal study 20030216 demonstrated robust evidence of significantly increased 36-month BMD in post-menopausal women with osteoporosis (T-score between minus 2.5 and minus 4) as measured by DEXA for 3902 patients treated with denosumab at the lumbar spine and total hip, compared to 3906 patients receiving placebo.

This was supported by data from the non-pivotal study 20040132 which demonstrated statistically significant increases in 24-month BMD in post-menopausal women with osteopenia (T-score between minus 1 and minus 2.5) for 166 patients treated with denosumab, at the lumbar spine, total hip, femoral neck, trochanter, distal radius and total body, compared to 166 patients who received placebo.

The pivotal study 20040135 found a statistically significant increase in 12-month BMD at the lumbar spine, femoral neck and total hip for 127 women with non-metastatic breast cancer receiving hormonal ablation therapy and treated with denosumab, compared to 125 women who received placebo; there was no statistically significant difference in fracture incidence between groups.

[51] Blade J, Samson D, Reece D. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and hematopoietic stem cell transplantation. Br J Haematol 1998; 102: 1115-1123.

The pivotal study 20040138 found a statistically significant increase in 24-month BMD at the lumbar spine, femoral neck and total hip for 734 men with non-metastatic prostate cancer receiving hormonal ablation therapy and treated with denosumab, compared to 734 receiving placebo; although there was a trend to reduced fracture incidence in men treated with denosumab, this did not achieve statistical significance other than for new vertebral fractures ($p = 0.0125$).

The extension, off-treatment phase of study 20040132 demonstrated that mean BMD at multiple assayed sites returned to pre-treatment levels, but was accompanied by biochemical markers suggestive of bone turnover higher than pre-treatment levels.

Although ongoing, data from the extension studies 20050233 and 20060289 support the continued efficacy of denosumab in increasing BMD at sites such as the lumbar spine and total hip; whether this corresponds with reduced fracture incidence is not yet clear.

The non-pivotal studies were generally supportive of the efficacy of denosumab (particularly in regard to BMD increases), demonstrated acceptable tolerability, and found non-inferiority of denosumab compared to conventional anti-resorptive therapy such as the bisphosphonates.

Safety

The pivotal trials contributed the majority of safety data available for denosumab; when complete, the ongoing extension studies are likely to add the safety database considerably.

The pivotal study in women with postmenopausal osteoporosis included a total of 7,762 women, of whom 3,886 received at least one dose of denosumab at the proposed dose of 60 mg. In total, 3093 women received all six doses.

The two pivotal studies in patients with breast or prostate cancer receiving hormonal ablation therapy included a total of 720 patients, of whom 900 received at least one dose of denosumab at the proposed dose of 60 mg. In total, 104 women received all four scheduled doses and 490 men received all six scheduled doses of denosumab.

The supporting trials provided additional exposures, including approximately 900 patients exposed to the active comparator alendronate. In total, the submitted studies include more than 7800 patients exposed to denosumab and approximately 13,000 patient-years of exposure.

Pivotal Studies

Study 20030216

Drug Exposure and Overview of Adverse Events

A total of 7,762 patients received at least one dose of the investigational product, of these 3,886 received denosumab. 3093/3886 patients (79.6%) in the denosumab group received all six doses, compared to 2886/3876 patients (74.5%) in the placebo group (Table 7).

Adverse events were very common and were experienced by 3607/3876 patients (93.1%) receiving placebo and 3605/3886 patients (92.8%) receiving denosumab **(**Table 8). The incidence of the most common AEs were similar between the two treatment groups, and included back pain (placebo versus denosumab: 34.6% versus 34.7%), arthralgia (20.2% versus 20.2%), hypertension (16.4% versus 15.8%) and nasopharyngitis (15.5% versus 14.5%). Indeed, the incidences of the twenty most common AEs were very similar between the two groups (Table 9**)**.

Episodes of pancreatitis appeared to be more common in the denosumab group (9 events in 8 patients) compared to placebo (4 events in 4 patients). In two cases, both had been treated

with denosumab, the episodes of pancreatitis led to death. There was no clear temporal relationship between dose and onset of pancreatitis and in all but one (who had been receiving denosumab for two years) there were significant risk factors to confound any direct causation by denosumab.

Table 7 - Exposure ot the investigational product (Study 20030216)

	Placebo	Denosumab 60 mg Q6M
Number of subjects randomized	3906	3902
Number of subjects receiving ≥ 1 dose of investigational product	3876	3886[a]
Number of injections (denosumab or placebo)		
1	214/3876 (5.5%)	204/3886 (5.2%)
2	194/3876 (5.0%)	165/3886 (4.2%)
3	211/3876 (5.4%)	165/3886 (4.2%)
4	153/3876 (3.9%)	117/3886 (3.0%)
5	218/3876 (5.6%)	142/3886 (3.7%)
6	2886/3876 (74.5%)	3093/3886 (79.6%)

Table 8 - Summary of adverse events (Study 20030216)

	Placebo (N=3876) n (%)	Denosumab 60 mg Q6M (N=3886) n (%)
Adverse events regardless of relationship		
All	3607 (93.1)	3605 (92.8)
Serious	972 (25.1)	1004 (25.8)
Fatal	90 (2.3)	70 (1.8)
Leading to study discontinuation	81 (2.1)	93 (2.4)
Leading to investigational product discontinuation	202 (5.2)	192 (4.9)
Adverse events related to investigational product[a]		
All	419 (10.8)	468 (12.0)
Serious	27 (0.7)	41 (1.1)
Fatal	1 (<0.1)	5 (0.1)
Leading to study discontinuation	7 (0.2)	13 (0.3)
Leading to investigational product discontinuation	37 (1.0)	36 (0.9)

AEs possibly caused by the investigational product were slightly more common in the denosumab group (12.0%) than placebo (10.8%). The majority were not considered serious. The most frequent treatment-related AEs were back pain (denosumab versus placebo: 1.1% versus 1.1%), arthralgia (0.9% versus 0.6%), headache (0.8% versus 0.6%) and nausea (0.7% versus 0.7%).

Table 9 - Adverse evemts by MedDRA preferred term (Study 20030216)

Preferred Term	Placebo (N=3876) n (%)	Denosumab 60 mg Q6M (N=3886) n (%)
Number of subjects reporting adverse events[a]	3607 (93.1)	3605 (92.8)
Back pain	1340 (34.6)	1347 (34.7)
Arthralgia	782 (20.2)	784 (20.2)
Hypertension	636 (16.4)	614 (15.8)
Nasopharyngitis	600 (15.5)	563 (14.5)
Pain in extremity	430 (11.1)	453 (11.7)
Osteoarthritis	442 (11.4)	436 (11.2)
Constipation	361 (9.3)	355 (9.1)
Influenza	335 (8.6)	331 (8.5)
Bronchitis	301 (7.8)	301 (7.7)
Musculoskeletal pain	291 (7.5)	297 (7.6)
Hypercholesterolaemia	236 (6.1)	280 (7.2)
Urinary tract infection	253 (6.5)	245 (6.3)
Headache	258 (6.7)	237 (6.1)
Cataract	253 (6.5)	229 (5.9)
Diarrhoea	236 (6.1)	228 (5.9)
Cystitis	225 (5.8)	228 (5.9)
Cough	238 (6.1)	224 (5.8)
Dizziness	218 (5.6)	217 (5.6)
Depression	221 (5.7)	213 (5.5)
Fall	250 (6.4)	205 (5.3)
Vertigo	187 (4.8)	195 (5.0)
Dyspepsia	212 (5.5)	178 (4.6)

Serious Adverse Events, Deaths and Discontinuations due to Adverse Events

The number of deaths during the 36-month observation period was lower for the denosumab group (70/3886 patients, 1.8%) than for placebo (90/3876 patients, 2.3%). Incidences of specific causes of death were similar between the two groups, with the most common being myocardial infarction (0.2%), pancreatic carcinoma (0.1%), cardiogenic shock (0.1%) and respiratory malignancy (0.1%). There were few instances of fatal adverse events judged possibly related to the investigational product. Of these, one death was recorded from the placebo group (adenocarcinoma) and five from the denosumab group (cerebellar tumour, myocardial infarction, ovarian cancer, and two of pancreatitis).

Serious adverse events (SAEs) were encountered with comparable frequency in both groups (972/3876 patients or 25.1% for placebo, 1004/3886 patients or 25.8% for denosumab). The most frequent SAEs in the denosumab group were osteoarthritis (denosumab versus placebo: 1.6% versus 2.0%), atrial fibrillation (0.9% versus 0.9%), pneumonia (0.9% versus 0.9%) and breast cancer (0.9% versus 0.6%). The incidence of SAEs considered possibly related to the investigational product was higher in the denosumab group (41/3886 patients, 1.1%) than for placebo (27/3876 patients, 0.7%). The most frequent of these were angina pectoris (4 patients, compared to 1 for placebo), breast cancer (4 patients, 1 for placebo), asthenia, cardiac failure and hypertension (each with 3 patients, none for placebo).

The rate of discontinuation due to adverse events was slightly higher in the placebo group (202/3876 patients, 5.2%) than for denosumab (192/3886 patients, 4.9%). The most common AEs causing discontinuation for the denosumab group were breast cancer (20 patients, compared to 10 for placebo), back pain (6 patients, compared to 10 for placebo), constipation (6 patients for each group) and headache (6 patients, compared to 4 for placebo).

Adverse Events of Special Interest and the Bone Biopsy Substudy

Adverse events of particular interest to be defined *a priori* included hypocalcaemia, cardiovascular adverse events, malignancies, infections, osteonecrosis of the jaw, hypersensitivity and delayed fracture healing.

Based on its mechanism of action, inhibitors of RANK have the potential to lower serum calcium. Adverse events of hypocalcaemia included the preferred terms "hypocalcaemia", "blood calcium decreased", "calcium ionized decreased" and "calcium deficiency". Abnormal laboratory findings without clinical significance were (at the investigator's discretion) not recorded as adverse events. No such events were recorded for the denosumab group, but were for 3 patients in the placebo group.

Cardiovascular AEs were balanced between the two treatment groups. The most frequent AEs in this system organ class were angina pectoris (2.6% denosumab, 2.2% placebo), atrial fibrillation (2.0% in each), palpitations (1.5% in each), cardiac failure (1.4% denosumab, 1.0% placebo) and arrhythmias (1.1% in each). Cardiovascular AEs were adjudicated by a blinded panel of cardiologists; there were no statistically significant differences in any term between the two groups.

Malignancies were slightly more common in the denosumab group (4.8%) compared to placebo (4.3%). The most common in the denosumab group were breast cancer (34 patients [0.9%] compared to 26 [0.7%] for placebo), basal cell carcinoma (30 patients [0.8%] compared to 35 [0.9%] for placebo) and colon cancer (11 patients [0.3%] compared to 8 [0.2%]) for placebo.

Infections were slightly less common the denosumab group (52.9%) than for placebo (54.4%). The most frequent were nasopharyngitis (14.5% denosumab, 15.5% placebo), influenza (8.5% denosumab, 8.6% placebo) and bronchitis (7.7% denosumab, 7.8% placebo).

No patient in either group experienced osteonecrosis of the jaw.

Adverse events potentially associated with hypersensitivity were infrequent and balanced between the two groups, with 50 patients (1.3%) experiencing this AE.

A total of 386 patients receiving denosumab and 465 patients receiving placebo recorded nonvertebral fractures. Two patients in each group experienced delayed healing and one patient (receiving placebo) experienced non-union. In the fracture healing substudy, 25 patients with a fracture of the distal radius were enrolled (8 received denosumab, 17 placebo). One patient in the denosumab group and two in the placebo group had delayed radiographic healing as judged by a blinded pair of radiographers.

A total of 29 patients treated with denosumab and 14 treated with placebo tested positively for anti-denosumab binding antibodies. None were neutralizing and no association with an alteration to the drug's safety or efficacy was noted.

A total of 92 patients who received at least one dose of the investigational product and provided consent had at least one evaluable bone biopsy taken. This subgroup resembled the general study population in terms of disposition, demographics and baseline disease characteristics; these patients yielded 115 biopsies (53 denosumab, 62 placebo) for evaluation. After 24 or 36 months of treatment with either placebo or denosumab, there was no evidence of osteomalacia, marrow fibrosis, woven bone or abnormal osteoid. Denosumab did not appear to impair mineralization of the matrix. Overall, 98 biopsies were evaluable for histomorphometry; a significant decrease in cortical porosity and increase in cortical bone mineral density was seen in the denosumab group at 24 months.

In order to estimate bone turnover, participants of the bone biopsy substudy were treated with courses of tetracycline or demeclocycline, drugs which are known to be incorporated into newly- mineralized bone during treatment. Both result in fluorescence when the biopsied bone is viewed under ultraviolet light. All 37 of the Month 24 biopsies collected from patients receiving placebo had both labels present, as did all 25 of the Month 36 biopsies from patients receiving placebo. Conversely, 11/31 of the Month 24 biopsies collected from the denosumab group and 8/21 of the Month 36 biopsies contained no label. This result is suggestive of reduced bone turnover and new bone mineralization, but the clinical meaning of this result is less clear.

A number of derived parameters reflecting denosumab's effect on bone were obtained from quantitative histomorphometry. Compared to placebo, "activation frequency" (the probability that a new remodelling cycle is initiated in trabecular bone), bone formation rate per bone surface, mineral apposition rate and mineralization lag time were all moderately reduced in patients receiving denosumab, as might be expected from the mechanism of action of the drug. Again, the clinical meaning of such results is not clear.

Laboratory Abnormalities and Vital Signs

No trends were noted in serum chemistry or haematology other than the expected decreases in calcium, phosphorus and total alkaline phosphatase.

Serum calcium levels fell slightly from Month 1 and remained mildly (but not clinically significantly) depressed throughout the study. Four patients in each treatment arm (0.1%) experienced a CTC Grade 2 decrease, and one receiving placebo had a CTC Grade 3 decrease.[52] Patients receiving denosumab showed an early trend to a mild decrease of serum phosphorus, normalizing around the 18 month datum. Both treatment groups experienced an early and sustained fall in alkaline phosphatase, but this was significant in the denosumab treatment group. Two patients in the denosumab group (0.2%) had a CTC Grade 3 increase in alkaline phosphatase.

There were no clinically significant changes to vital signs in either treatment group.

Study 20040135

Drug Exposure and Overview of Adverse Events

A total of 249 women with non-metastatic breast cancer received at least one dose of the investigational product and were included in the safety set, of these 129 received denosumab. A slightly greater proportion of patients in the denosumab group (104/129 patients [81%]) received all four doses of denosumab (at zero, 6, 12 and 18 months), compared to 94/120 patients (78%) in the placebo group (Table 10).

[52] CTC: Common Terminology Criteria (for Adverse Events) utilises a 5-point scale generally corresponding mild, moderate, severe, life-threatening and death.

Table 10 - Exposure to the investigational product (Study 20040135)

	Placebo (N=120)	Denosumab 60 mg Q6M (N=129)	All (N=249)
Number of denosumab or placebo doses - n (%)			
1	14 (12)	10 (8)	24 (10)
2	7 (6)	7 (5)	14 (6)
3	5 (4)	8 (6)	13 (5)
4	94 (78)	104 (81)	198 (80)

Adverse events were equally common in both groups, and were experienced by 108/120 patients (90.0%) receiving placebo and 117/129 patients (90.7%) receiving denosumab (Table 11). The incidence of the most common AEs were well matched between the two treatment groups, and included arthralgia (25.0% placebo, 24.0% denosumab), extremity pain (11.7% versus 14.7%), back pain (12.5% versus 14.0%) and fatigue (14.2% versus 13.2%).

Table 11 - Adverse events witn an incidence of at least 5% (Study 20040135)

Preferred Term	Placebo (N=120) n (%)	Denosumab 60 mg Q6M (N=129) n (%)
Number of Subjects Reporting Adverse Events	108 (90.0)	117 (90.7)
Arthralgia	30 (25.0)	31 (24.0)
Pain in extremity	14 (11.7)	19 (14.7)
Back pain	15 (12.5)	18 (14.0)
Fatigue	17 (14.2)	17 (13.2)
Constipation	11 (9.2)	15 (11.6)
Cough	5 (4.2)	13 (10.1)
Insomnia	14 (11.7)	12 (9.3)
Headache	9 (7.5)	11 (8.5)
Myalgia	5 (4.2)	11 (8.5)
Shoulder pain	4 (3.3)	11 (8.5)
Nausea	11 (9.2)	10 (7.8)
Rash	6 (5.0)	10 (7.8)
Upper respiratory tract infection	6 (5.0)	10 (7.8)
Sinusitis	4 (3.3)	9 (7.0)
Vulvovaginal dryness	3 (2.5)	9 (7.0)
Anxiety	6 (5.0)	8 (6.2)
Oedema peripheral	5 (4.2)	8 (6.2)
Vomiting	6 (5.0)	8 (6.2)
Depression	11 (9.2)	7 (5.4)
Dyspnoea	5 (4.2)	7 (5.4)
Hot flush	8 (6.7)	7 (5.4)
Hypoaesthesia	4 (3.3)	7 (5.4)
Muscle spasms	6 (5.0)	7 (5.4)
Musculoskeletal chest pain	6 (5.0)	7 (5.4)
Urinary tract infection	5 (4.2)	7 (5.4)
Arthritis	6 (5.0)	5 (3.9)
Bone pain	8 (6.7)	5 (3.9)
Bronchitis	7 (5.8)	5 (3.9)
Diarrhoea	9 (7.5)	5 (3.9)
Breast pain	6 (5.0)	3 (2.3)
Gastrooesophageal reflux disease	8 (6.7)	2 (1.6)
Hypertension	7 (5.8)	2 (1.6)

AEs possibly related to study treatment were equally common in the denosumab (25%) and placebo (26%) groups. Those most frequent were pain in an extremity (2% denosumab, 4% placebo), arthralgia (5% denosumab, 2% placebo), bone pain (1% denosumab, 4% placebo) and fatigue (2% each). No SAEs or AEs leading to withdrawal were considered possibly related to the investigational product.

Serious Adverse Events, Deaths and Discontinuations due to Adverse Events

One death was recorded in each treatment arm during the 24 observational months of study. Both were attributed to progression of disease (breast cancer) and neither was considered to be related to the investigational product.

Serious adverse events were more common for patients in both groups than was the case for either of the previous pivotal trials, probably reflecting the increased burden of morbidity in this patient population. SAEs were more common among patients treated with denosumab (19 patients, 15%) than with placebo (11 patients, 9%). None of the SAEs were considered related to study treatment. No single SAE was reported for more than two patients. Osteoarthritis was recorded for two patients receiving denosumab, cholelithiasis for two patients receiving placebo, and arthritis, cholecystitis and transient ischaemic attack in one patient in each group. Two patients, both receiving placebo, withdrew due to SAEs (interstitial pneumonitis, and multiple metastases respectively).

In total, two patients (2%) receiving denosumab and 5 patients (4%) receiving placebo withdrew from the investigational product due to adverse events. None was considered to be related to the investigational product.

Adverse Events of Special Interest

The only adverse events (AEs) of special interest were instances of hypocalcaemia or adverse events possibly a clinical manifestation of hypocalcaemia. No adverse events of hypocalcaemia were recorded in either group. Those AEs which may have represented clinical manifestations of hypocalcaemia were more common in the denosumab group (6%) than for placebo (3%); these included hypoaesthesia, paraesthesia and oral paraesthesia. None was considered serious.

Two patients from the denosumab group were positive for post-dose anti-denosumab binding antibodies, and a further one patient in the placebo group has pre-existing binding antibodies. These were transient and non-neutralizing in all three cases, and not associated with any treatment-related adverse events.

Laboratory Abnormalities and Vital Signs

Overall, laboratory results from the treatment period supported the view that denosumab does not result in clinically meaningful changes to important laboratory parameters. Consistent with the previous experience from preclinical and clinical trials, the only changes seen were again the expected decreases in serum calcium, phosphorus and alkaline phosphatase.

Corrected calcium fell in the denosumab group from the first post-treatment measurement by minus 3.0% compared to an increase of 0.2% for the placebo group. The difference was neither statistically significant nor sustained. Two patients in each group experienced CTC Grade 1 toxicities of hypocalcaemia.

Mean serum phosphorus followed a similar pattern, but the fall in the denosumab group was more rapid (-8.2% at Month 1, compared to +1.3% for placebo) and more sustained. One

patient receiving denosumab recorded a CTC Grade 2 toxicity of hypophosphataemia without clinical sequelae.

Mean serum alkaline phosphatase values were similar in both groups initially but showed a clear trend to a sustained decrease in the denosumab group compared to placebo. One patient recorded a CTC Grade 3 toxicity of elevated alkaline phosphatase at Month 24, accounting for the relatively wide confidence interval at this time.

There were no significant changes to vital signs in either group during the trial. ECG data was not recorded.

Study 20040138

Drug Exposure and Overview of Adverse Events

A total of 1456 men with low bone mass and non-metastatic prostate cancer treated with hormonal ablation received at least one dose of the investigational product and were included in the safety set, of these 731 received denosumab. A slightly greater proportion of patients in the denosumab group (490/731 patients [67%]) received all six doses, compared to 450/725 patients (62%) in the placebo group (Table 12).

Adverse events were equally common in both groups, and were experienced by 627/725 patients (86.5%) receiving placebo and 638/731 patients (87.3%) receiving denosumab (Table 13). The incidence of the most common AEs were well matched between the two treatment groups, with the most common being arthralgia (denosumab versus placebo: 12.6% versus 11.0%), back pain (11.1% versus 10.2%), constipation (10.0% versus 10.3%) and pain in an extremity (9.0% versus 7.0%).

Table 12 - Exposure to the investigational product (Study 20040138)

	Placebo	Denosumab 60 mg Q6M
Number of subjects randomized	734	734
Number of subjects receiving ≥ 1 dose of investigational product	725	731[a]
Number of injections (denosumab or placebo)		
1	54/725 (7.4%)	45/731 (6.2%)
2	44/725 (6.1%)	31/731 (4.2%)
3	43/725 (5.9%)	40/731 (5.5%)
4	99/725 (13.7%)	97/731 (13.3%)
5	35/725 (4.8%)	28/731 (3.8%)
6	450/725 (62.1%)	490/731 (67.0%)

AEs possibly related to study treatment were equally common in the denosumab (8.5%) and placebo (9.0%) groups. The most frequent of these was fatigue (denosumab versus placebo: 1.1% versus 0.4%), with no other treatment-related adverse even reported with a frequency of more than 1%. No SAEs or AEs leading to withdrawal were considered possibly related to the investigational product.

Table 13 - Adverse events with an incidence of at least 5% (Study 20040138)

Preferred Term	Placebo (N=725) n (%)	Denosumab 60 mg Q6M (N=731) n (%)
Number of subjects reporting adverse events[a]	627 (86.5)	638 (87.3)
Arthralgia	80 (11.0)	92 (12.6)
Back pain	74 (10.2)	81 (11.1)
Constipation	75 (10.3)	73 (10.0)
Pain in extremity	51 (7.0)	66 (9.0)
Hypertension	51 (7.0)	57 (7.8)
Oedema peripheral	48 (6.6)	53 (7.3)
Nasopharyngitis	45 (6.2)	47 (6.4)
Fatigue	45 (6.2)	44 (6.0)
Dizziness	31 (4.3)	41 (5.6)
Musculoskeletal pain	26 (3.6)	41 (5.6)
Diarrhoea	39 (5.4)	40 (5.5)
Hot flush	32 (4.4)	38 (5.2)
Urinary tract infection	32 (4.4)	37 (5.1)

Serious Adverse Events, Deaths and Discontinuations due to Adverse Events

A relatively large but balanced number of deaths occurred in each group; 46/725 patients (6.3%) treated with placebo and 44/731 patients (6.0%) treated with denosumab recorded fatal adverse events during the 36 months of observation. The causes of death varied widely and all but one were judged unrelated to the investigational product. One fatal myocardial infarction was recorded in a patient receiving placebo, felt before unblinding to be possibly treatment-related. The relatively larger number of deaths in this pivotal trial likely reflects the older mean age and burden of comorbidity of this selected population.

Serious adverse events were relatively common in both groups, again probably reflecting a greater mean age and burden of disease. SAEs were more common among patients treated with denosumab (253 patients, 34.6%) than with placebo (222 patients, 30.6%). The incidence of treatment-related SAEs was low and similar in both groups (4 patients [0.6%] for denosumab, 3 patients [0.4%] for placebo). Cardiac system disorders were the most common class of SAEs and were slightly more common in the placebo group (10.3%) than for those receiving denosumab (9.4%) (Table 14). Nervous system disorders were the next most common class (6.8% denosumab, 4.8% placebo) followed by infections and infestations (5.9% denosumab, 4.6% placebo).

In total, 49 patients (6.7%) receiving denosumab and 47 patients (6.5%) receiving placebo discontinued the investigational product use due to adverse events. The most common of these were protocol-mandated discontinuations due to bony metastasis, experienced by 8 patients receiving denosumab and 9 patients receiving placebo. Only 5 patients treated with denosumab and 1 treated with placebo discontinued the study drug as a result of treatment-related adverse events.

Adverse Events of Special Interest

A number of clinically significant adverse events were defined as being of special interest.

MedDRA preferred terms for clinical findings which might reflect hypocalcaemia were audited.[53] One event of hypocalcaemia was recorded, in a patient receiving denosumab. This was both a severe (CTC Grade 3 toxicity) and serious adverse event, but was not considered

[53] MedDRA = Medical Dictionary for Regulatory Activities.

related to study treatment. This patient developed hypocalcaemia on study day 12 and was subsequently diagnosed with primary pancreatic cancer, a malignancy leading to death two months later. A total of 21 patients receiving denosumab and 15 receiving placebo reported adverse events of hypoaesthesia or paraesthesia. None had a high-grade toxicity of hypocalcaemia at the time so a relationship seems unlikely.

Cardiovascular safety was assessed by an external panel of expert cardiologists. The overall crude incidence of positively-adjudicated serious cardiovascular adverse events was 10.9% for patients treated with denosumab compared to 11.0% for those treated with placebo. By individual MedDRA preferred term within this class, none achieved a significant hazard ratio for denosumab over placebo.

A total of 119 patients (16.3%) treated with denosumab recorded an adverse event in the neoplasm system organ class, compared to 86 patients (11.9%) treated with placebo. AEs confirmed as a new primary malignancy were similarly frequent in both groups (37 patients [5.1%] treated with denosumab, 33 patients [4.6%] treated with placebo).

Adverse events and SAEs in the infection and infestation system organ class were more common in the group treated with denosumab (257 and 43 patients) than in those treated with placebo (226 and 33 patients). Nine events of diverticulitis were recorded in the denosumab group and none for placebo. The investigator demonstrated that the standardized incidence rate of diverticulitis was comparable to that expected in a non-institutionalized male population aged over 65 in the US.

Events of osteonecrosis of the jaw were of special interest, but none was recorded during the study.

The incidence of hypersensitivity was low and balanced between the groups (two patients receiving denosumab, one receiving placebo). The incidence of other AEs possibly related to drug sensitivity were similarly balanced (0.7% denosumab, 1.1% placebo).

Table 14 - Serious adverse events with an incidence of at least 0.5% (Study 20040138)

Preferred Term	Placebo (N=725) n (%)	Denosumab 60 mg Q6M (N=731) n (%)
Number of subjects reporting serious adverse events	222 (30.6)	253 (34.6)
Myocardial infarction	18 (2.5)	14 (1.9)
Pneumonia	11 (1.5)	11 (1.5)
Atrial fibrillation	8 (1.1)	11 (1.5)
Cerebrovascular accident	12 (1.7)	10 (1.4)
Coronary artery disease	11 (1.5)	9 (1.2)
Transient ischaemic attack	4 (0.6)	9 (1.2)
Syncope	5 (0.7)	8 (1.1)
Dyspnoea	3 (0.4)	8 (1.1)
Cardiac failure congestive	10 (1.4)	6 (0.8)
Urinary retention	3 (0.4)	6 (0.8)
Dehydration	2 (0.3)	6 (0.8)
Osteoarthritis	1 (0.1)	6 (0.8)
Pulmonary embolism	1 (0.1)	6 (0.8)
Colon cancer	4 (0.6)	5 (0.7)
Chronic obstructive pulmonary disease	3 (0.4)	5 (0.7)
Rib fracture	1 (0.1)	5 (0.7)
Sick sinus syndrome	1 (0.1)	5 (0.7)
Diverticulitis	0 (0.0)	5 (0.7)
Hypotension	0 (0.0)	5 (0.7)
Non-cardiac chest pain	0 (0.0)	5 (0.7)
Acute myocardial infarction	5 (0.7)	4 (0.5)
Anaemia	5 (0.7)	4 (0.5)
Hypertension	5 (0.7)	4 (0.5)
Angina pectoris	4 (0.6)	4 (0.5)
Cardiac arrest	4 (0.6)	4 (0.5)
Cholelithiasis	4 (0.6)	4 (0.5)
Prostate cancer	4 (0.6)	4 (0.5)
Renal failure	4 (0.6)	4 (0.5)
Acute coronary syndrome	3 (0.4)	4 (0.5)
Bladder cancer	3 (0.4)	4 (0.5)
Bradycardia	3 (0.4)	4 (0.5)
Deep vein thrombosis	3 (0.4)	4 (0.5)
Cardiac failure	2 (0.3)	4 (0.5)
Pleural effusion	1 (0.1)	4 (0.5)
Cholecystitis	0 (0.0)	4 (0.5)
Metastases to bone	10 (1.4)	3 (0.4)
Fall	5 (0.7)	3 (0.4)
Renal failure acute	5 (0.7)	3 (0.4)
Death	5 (0.7)	2 (0.3)
Gastrointestinal haemorrhage	5 (0.7)	2 (0.3)
Cellulitis	4 (0.6)	2 (0.3)
Small intestinal obstruction	4 (0.6)	1 (0.1)
Myocardial ischaemia	6 (0.8)	0 (0.0)
Chest pain	4 (0.6)	0 (0.0)
Sepsis	4 (0.6)	0 (0.0)
Septic shock	4 (0.6)	0 (0.0)

Complications of fracture healing were of special interest. A total of 44 patients in each treatment group reported a nonvertebral fracture, with no reports from either group of delayed healing or non-union.

Four patients tested positive for anti-denosumab binding antibodies. Two patients in the placebo group were positive for pre-existing antibodies and one patient from each treatment

group developed binding antibodies during the trial. All cases were non-neutralizing, were transient, and none was associated with a treatment-related adverse event.

Laboratory Abnormalities and Vital Signs

Consistent with previous experience, denosumab treatment was associated with an early fall in corrected calcium which was not accompanied by clinical sequelae. By Month 36, the interquartile range of percentage change in calcium was minus 1.0% to +5.6% for the denosumab group and minus 2.0% to +4.8% for placebo. No patient had a CTC Grade 3 or 4 toxicity of hypocalcaemia during the study.

An early and sustained modest fall in median serum phosphorus was again noted in this study. Three patients receiving denosumab had a CTC Grade 3 decrease in serum phosphorus, and one had a CTC Grade 4 decrease. The latter case was associated with jaundice, worsening of prostate cancer and metastasis to the liver.

Importantly, treatment with denosumab appeared no different from treatment with placebo in terms of serum prostate-specific antigen or serum testosterone.

No other marked differences in biochemistry or haematology were noted for the denosumab group compared to those receiving placebo.

Denosumab treatment appeared to have no clinically meaningful effect on vital signs or the physical examination. ECG data was not recorded.

Extension and Longer-term Studies

Study 20040132

Drug Exposure and Overview of Adverse Events

All of the 256 patients (of whom 128 had received denosumab and 128 placebo) entering the off-treatment phase were included in the safety analysis. Overall, the adverse event profiles in the two initial treatment groups were very similar during the 12 months of off-treatment reporting.

In total, 97/128 patients (75.8%) who had received denosumab and 87/128 patients (68.0%) who had received placebo reported at least one adverse event. The most common were nasopharyngitis (9.4% denosumab, 7.8% placebo), back pain (7.8% denosumab, 12.5% placebo) and arthralgia (7.8% denosumab, 10.2% placebo).

Deaths, Serious Adverse Events and Discontinuations due to Adverse Events

There were no deaths or withdrawals due to adverse events during the off-treatment period.

Overall, 3/128 patients (2.3%) who had received denosumab and 6/128 patients (4.7%) who had received placebo experienced a SAE. One patient who had received denosumab had an SAE considered possibly related to the investigational product. This was a metastatic atypical spindle cell carcinoid tumour occurring 31 months after initial treatment and 7 months into the off-treatment period.

Adverse Events of Special Interest

A similar proportion of both treatment groups experienced an infection during the off-treatment period (31.3% denosumab, 29.7% placebo). The most frequent of these were nasopharyngitis, sinusitis and bronchitis. No opportunistic infections were observed.

No patients recorded an adverse event of osteonecrosis of the jaw nor were there any instances of fracture healing complications.

Four patients in both groups recorded an adverse event of neoplasia, of these, two in each group, were considered serious; for the denosumab group these included meningioma and metastatic carcinoid, and in the placebo group benign ovarian tumour and breast cancer.

In total, 6/128 patients (4.7%) who had received denosumab recorded a fracture as an adverse event (although only two of these met the definition of clinical fracture). 3/128 patients (2.3%) who had received placebo experienced a fracture (of whom two met the definition of clinical fracture).

Laboratory Abnormalities, Vital Signs and ECG

No meaningful trends in serum chemistry (including calcium, phosphorus and alkaline phosphatase) were noted nor were there any significant changes to vital signs or the physical examination.

Study 20050233

Drug Exposure and Overview of Adverse Events

All 200 of the enrolled patients received at least one dose of denosumab and were included in the safety analysis. Given the open-label design, a concurrent control group was not available for comparison. In general, the types, rates and severities of adverse events reflected those observed in other studies of denosumab's safety in women with low bone mass.

Adverse events were moderately common, and were experienced by 126/200 patients (63%). Those most common were arthralgia (8.5%), upper respiratory tract infection (7.0%) and back pain (5.5%).

Adverse events possibly related to treatment occurred in 6% of patients.

Deaths, Serious Adverse Events and Discontinuations due to Adverse Events

A single death was recorded during the study so far. One patient (0.3%) died unexpectedly 3 weeks after the second dose; cause of death was unknown and attempts to collect further data concerning it were unsuccessful.

Serious adverse events were reported for 12 patients (6.0%). Two of these were considered to be possibly treatment-related, including one of breast cancer in situ (five months after receiving the first and only dose of denosumab) and one of staphylococcal bacteraemia (six weeks after receiving the second dose of denosumab).

Adverse events led to discontinuation in five patients (2.5%). No event occurred in more than one patient.

Adverse Events of Special Interest

No AEs of hypocalcaemia were recorded, and two patients (1%) reported symptoms that might possibly have reflected hypocalcaemia (hypoaesthesia and paraesthesia). A total of 48 patients (24%) experienced an infection or infestation, of which the most common were upper respiratory tract infections (7.0%), sinusitis (4.5%) and urinary tract infection (2.5%). No opportunistic infections were reported. No cases of osteonecrosis of the jaw were recorded, nor were there reports of delayed fracture healing. A total of 10 patients (5%) developed a neoplasm during the 12 months, of which one was considered possibly related to treatment.

All patients tested post-baseline for anti-denosumab binding antibodies were negative.

Laboratory Abnormalities and Vital Signs

No clinically significant changes in chemistry or haematology were noted other than the expected fall in serum phosphorus, total alkaline phosphatase and albumin-corrected calcium. There were no significant changes for vital signs or the physical examination.

Study 20060289

Drug Exposure and Overview of Adverse Events

This trial is an open-label extension phase of Study 20030216. The safety parameters of this pivotal trial are analysed above. The study report supplied in the submission is in interim synopsis form only, but when complete the evaluator considers this will provide a considerable portion of the available five- year safety data for denosumab treatment of postmenopausal osteoporosis. Only incomplete data from the first twelve months of the extension phase is discussed here.

It would seem that 4307 patients had been exposed to at least one dose of denosumab and should be included in the safety analysis, although this is not stated explicitly in the draft synopsis.

Deaths, Serious Adverse Events and Discontinuations due to Adverse Events

Six deaths were recorded in the 12 months of extension data summarized in the synopsis. The cause of death was known for three (gastrointestinal carcinoma, metastatic gallbladder cancer and malignant lung neoplasm). None was considered related to drug treatment.

The incidence of SAEs is quoted as 1.9%, which would appear to be significantly lower than that of the preceding Study 20030216. The more common adverse events were in the System Organ Classes (SOC) *Musculoskeletal and Connective Tissue Disorders* (16 patients), *Neoplasms Benign, Unknown or Malignant* (15 patients) and *Infections or Infestations* (13 patients).

Discontinuations due to adverse events are not stated.

Non-pivotal Studies in Post-Menopausal Osteoporosis

Study 20040132

Drug Exposure and Overview of Adverse Events

A total of 329 post-menopausal women with osteopenia received at least one dose of the investigational product and were included in the safety set, of whom 164 received denosumab; 139/164 patients (85%) in the denosumab group received all four doses, as did 141/165 patients (85%) in the placebo group (Table 15).

Table 15 - Summary of exposure to the investigational product (Study 20040132)

	Placebo (N=165)	Denosumab 60 mg Q6M (N=164)	All (N=329)
Number of denosumab or placebo doses - n (%)			
1	11 (7)	7 (4)	18 (5)
2	8 (5)	11 (7)	19 (6)
3	5 (3)	7 (4)	12 (4)
4	141 (85)	139 (85)	280 (85)

Adverse events were again exceedingly common, and were experienced by 157/165 patients (95.2%) receiving placebo and 156/164 patients (95.1%) receiving placebo (Table 16). The incidence of the most common AEs were well matched between the two treatment groups, and included arthralgia (25.5% placebo, 25.0% denosumab), nasopharyngitis (18.8%, 22.0%), and back pain (20.0%, 20.1%).

AEs possibly related to study treatment were slightly more common in the denosumab group (15%) than for placebo (12%). Those most frequent were nausea (4% denosumab, 2% placebo), rash (2% denosumab, 0% placebo), headache (1% denosumab, 2% placebo) and myalgia (2% denosumab, 1% placebo). No SAEs or AEs leading to withdrawal were considered possibly related to the investigational product.

Table 16 - Adverse events with an incidence of at least 5% (Study 20040132)

Preferred Term	Placebo (N=165) n (%)	Denosumab 60 mg Q6M (N=164) n (%)
Number of Subjects Reporting Adverse Events	157 (95.2)	156 (95.1)
Arthralgia	42 (25.5)	41 (25.0)
Nasopharyngitis	31 (18.8)	36 (22.0)
Back pain	33 (20.0)	33 (20.1)
Headache	19 (11.5)	26 (15.9)
Pain in extremity	20 (12.1)	24 (14.6)
Upper respiratory tract infection	22 (13.3)	19 (11.6)
Constipation	8 (4.8)	18 (11.0)
Urinary tract infection	17 (10.3)	18 (11.0)
Shoulder pain	10 (6.1)	17 (10.4)
Nausea	12 (7.3)	16 (9.8)
Influenza	18 (10.9)	15 (9.1)
Pharyngolaryngeal pain	5 (3.0)	15 (9.1)
Diarrhoea	7 (4.2)	14 (8.5)
Rash	5 (3.0)	14 (8.5)
Insomnia	15 (9.1)	13 (7.9)
Muscle spasms	13 (7.9)	12 (7.3)
Cough	5 (3.0)	11 (6.7)
Myalgia	12 (7.3)	11 (6.7)
Depression	6 (3.6)	10 (6.1)
Sinusitis	17 (10.3)	10 (6.1)
Abdominal pain	7 (4.2)	9 (5.5)
Dyspepsia	10 (6.1)	9 (5.5)
Gastrooesophageal reflux disease	6 (3.6)	9 (5.5)
Procedural pain	5 (3.0)	9 (5.5)
Dizziness	9 (5.5)	7 (4.3)
Fatigue	12 (7.3)	7 (4.3)
Hypertension	14 (8.5)	6 (3.7)
Hypoaesthesia	9 (5.5)	5 (3.0)

Serious Adverse Events, Deaths and Discontinuations due to Adverse Events

No deaths were recorded during the treatment period.

Serious adverse events were more common for patients treated with denosumab (18 patients, 11%) than with placebo (9 patients, 6%). The most common SAEs were pneumonia (3 patients, all receiving denosumab), diverticulitis, osteoarthritis and sepsis (2 patients for each, all receiving denosumab). None was considered possibly related to treatment with the investigational product, and no patient withdrew from the study as the result of an SAE. The major cause of the imbalance between the two groups was the *Infections and Infestations* SOC, which was only represented by (eight) patients receiving denosumab. The investigator argues that all events were classified as serious because of the need for hospitalization, but that they occurred six to twelve months after the initial administration of the investigational product (in fact, denosumab), were community-acquired infections clinically, and where

organisms were cultured, the causative pathogens were typical of community-acquired infection. In particular, no opportunistic infections were reported.

In total, five patients (3%) receiving denosumab and 6 patients (4%) receiving placebo withdrew from the investigational product due to adverse events. None was considered to be related to the investigational product. One patient receiving denosumab and two receiving placebo withdrew from the study as a result of adverse events.

Adverse Events of Special Interest

The only AEs defined *a priori* as being of special interest were hypocalcaemia and fractures. No adverse events of confirmed and clinically significant hypocalcaemia were recorded. AEs that were considered possible clinical manifestations of hypocalcaemia were in fact more common in the placebo group (13 patients, 7.9%) than for denosumab (8 patients, 4.9%). Fractures were more common in the placebo group (14 patients, 9%) compared with the denosumab group (9 patients, 6%). The foot was the most common site of fracture (5 patients in each group).

Two patients receiving denosumab and three receiving placebo were positive for low levels of anti-denosumab binding antibodies. All were non-neutralizing and none experienced an adverse event that could be associated with the detection of binding antibodies.

Laboratory Abnormalities, Vital Signs and ECG

The experience with laboratory abnormalities was similar to that of the earlier pivotal trial, namely that there were no significant trends seen in chemistry or haematology other than the expected decreases in serum calcium, phosphorus and total alkaline phosphatase.

For patients receiving denosumab, serum calcium fell from the one month datum and remained decreased relative to those treated with placebo. There was a trend to normalization and at 24 months the difference was not large (-1.5% for denosumab, -0.7% for placebo). Two patients in the denosumab group experienced a CTC Grade 2 toxicity of hypocalcaemia. There were no relevant adverse events or QTc changes that suggested clinical significance to either instance.

The experience with serum phosphorus was similar. The mean for patients receiving denosumab was rapidly and moderately reduced, followed by a trend to normalization over time. Twelve patients receiving denosumab had CTC Grade 2 hypophosphataemia, and one patient receiving placebo. None were associated with clinical sequelae.

Alkaline phosphatase assays had similar findings to the earlier pivotal trial, in that there was a significant decrease by Month 6, which remained for the duration of the study.

High Grade (3 or 4) haematological or chemical toxicities were recorded for 4 patients receiving denosumab and 6 patients receiving placebo. One patient treated with denosumab recorded a potassium concentration of 9.4 mmol/L that was very likely an error resulting from a haemolysed sample (confirmed by the laboratory and a repeat assay within a week was normal).

There were no clinically meaningful changes to vital signs or body weight in either group.

ECGs were taken at baseline and Months 1, 12, 18 and 24. The proportion of patients with clinically meaningful prolongation of the Bazett-corrected QT interval was not significantly different between the two groups.

Study 20050141

A total of 1179 patients received the investigational product and were included in the safety analysis. Of these, 593 received denosumab and 586 received alendronate. Adverse events were reported in 480/593 (81%) patients treated with denosumab and 482/586 (82%) patients treated with alendronate. The most common adverse events were arthralgia (denosumab versus alendronate: 12.6% versus 9.6%), nasopharyngitis (7.6% versus 7.3%) and back pain (7.1% versus 9.6%). Of those events thought to be treatment-related, the most frequent were dyspepsia (3.0% versus 2.9%), arthralgia (1.9% versus 0.9%) and headache (1.7% versus 0.9%).

The rates of discontinuation due to adverse events were small and similar between the groups (4.4% denosumab, 3.8% alendronate). Serious adverse events were infrequent and similar, and were experienced by 34/593 (6%) patients treated with denosumab and 37/586 (6%) treated with alendronate. No SAEs were considered possibly related to treatment in the denosumab group. There was one death in each group, neither of which was considered related to treatment.

There were no clinically significant changes in laboratory parameters other than those already established in the safety profile of the drug. In particular, there was only one denosumab-treated patient with a CTC Grade 2 hypocalcaemia, which was not associated with symptoms and normalized at subsequent visits.

Study 20050179

A total of 247 patients received at least one dose of the investigational product and were included in the safety analysis. Of these, 83 received denosumab, 82 received alendronate and 82 received placebo. Adverse events were reported in 71/83 (86%) patients treated with denosumab, in 71/82 (87%) patients treated with alendronate and in 74/82 (90%) patients treated with placebo. The most common adverse events were constipation (18.1% denosumab, 16.0% alendronate, 14.5% placebo), influenza (16.9%, 12.3%, 18.1%) and extremity pain (12.0%, 9.9%, 9.6%). Potentially treatment-related AEs were most common in the alendronate group (44.4%) and least in the denosumab group (31.3%).

Rates of discontinuation due to adverse events were small and similar between the groups (6.0% denosumab, 3.7% alendronate, 2.4% placebo). Serious adverse events were least frequent in the denosumab group (2 patients) compared to alendronate (5 patients) and placebo (5 patients). No patients died during the study.

There were no clinically significant changes in laboratory parameters other than those already established in the safety profile of the drug.

Study 20050234

In all, 502 patients received at least one dose of the investigational product and were evaluated for safety. Of these, 249 had received alendronate and 253 received denosumab. Overall, the adverse event profiles in the two groups were very similar. Specifically, there were no significant safety implications noted for patients transitioning from alendronate to denosumab. Adverse events were experienced by 197/253 (77.9%) patients treated with denosumab, and by 196/249 (78.7%) treated with alendronate. Common adverse events included nasopharyngitis (denosumab versus alendronate: 13.4% versus 10.8%), back pain (10.7% versus 11.6%) and bronchitis (6.3% versus 5.6%). The rate of treatment-related adverse events was 13.0% in each group.

The proportion of patients who discontinued the investigational product (2.8% denosumab, 2.0% alendronate) and of those who withdrew from the study (1.2% denosumab, 0.8% alendronate) was comparable. Serious adverse events occurred in 15 patients treated with

denosumab and 16 with alendronate; of these only one episode of atrial fibrillation (in an alendronate-treated patient) was considered possibly related to treatment. There was one death (in the denosumab group) from cerebrovascular accident, considered unrelated to treatment.

Bone histology was evaluable for 36 of the 39 patients who entered a bone biopsy substudy. There were no pathological findings in the 15 denosumab-treated patients, nor did treatment with denosumab appear to impair matrix mineralization.

As was the case in the pivotal trial Study 20030216, those patients enrolled in the bone biopsy substudy were treated with tetracycline and demeclocycline. All 21 of the biopsied patients receiving alendronate had both labels present at 12 months, whereas 3/15 patients receiving denosumab had no label present.

Although the number of evaluable biopsies was small, the derived histomorphometric parameters of activation frequency, bone formation rate per bone surface, mineralization apposition rate and mineralization lag time were all moderately reduced in patients receiving denosumab compared to alendronate. The clinical meaning of such a comparison is not clear.

Study 20060232

At the date of data cut-off (May 2008), a total of 203 patients had received at least a dose of the investigational product and were included in the safety analysis. This study report was presented as an interim synopsis only, with an obligation to report only fatalities or serious adverse events.

By data cut-off, seven patients had discontinued the investigational product. No serious adverse events or deaths had yet been recorded.

Study 20060237

A total of 310 post-menopausal women with osteoporosis received at least one dose of denosumab and were analysed for safety, of these 154 received the drug from a vial and 156 from a prefilled syringe. Overall, 84/154 (54%) patients who had received denosumab from a vial and 101/156 (64.7%) patients who had received the drug from a prefilled syringe experienced an adverse event. Most of these were mild or moderate in severity. The most frequent were arthralgia (3.9% vial, 5.8% prefilled syringe), upper respiratory tract infection (1.3%, 5.8%) and back pain (5.2%, 4.5%).

The incidence of SAEs was similar between the two groups (3 patients using the vial, 5 patients using the prefilled syringe). The rate of withdrawals due to adverse events was also very similar between the two groups. Three patients had SAEs possibly related to treatment, including one episode of breast cancer (vial), one of aortic stenosis (prefilled syringe) and one of pancreatic cancer (prefilled syringe). No patients died during the study.

There were no consistent trends in serum chemistry of haematology, nor were any adverse events of hypocalcaemia noted.

Trials for Other Indications

The submission included safety data from five trials for indications other than those being sought by the sponsor. These safety data are not discussed in this AusPAR except for the observation that in Study 20050134, one patient developed osteonecrosis of the jaw which was considered unrelated to study treatment. This patient had a prior two-year exposure to zoledronate, a dental extraction one year prior to study enrolment and prior radiotherapy (all of which are acknowledged risk factors for osteonecrosis of the jaw). A screening dental

examination 9 days after the initial dose of denosumab revealed osteonecrosis at the site of the previous dental extraction. It was asserted that the condition was probably of several months' duration at this point, so causation appears unlikely.

Safety Conclusions

Safety was evaluated in adequate numbers, including a population from the pivotal studies of 3886 women with postmenopausal osteoporosis and 860 patients with non-metastatic breast or prostate cancer who were receiving hormonal ablation therapy, all of whom were exposed to at least a single dose of denosumab at the proposed dose of 60 mg.

Denosumab was generally well tolerated in the postmenopausal population and the hormonal ablation therapy population. There were no significant differences in the most common adverse events (back pain, arthralgia, hypertension, nasopharyngitis, and extremity pain) between the treatment and placebo groups.

In the two large studies in populations with post-menopausal osteoporosis, deaths were less common in the denosumab group (n=70, 1.7%) than the placebo group (n=90, 2.2%). In the trials in patients with breast or prostate cancer receiving hormonal ablation therapy, deaths were also less common in the denosumab group (n=45, 5.2%) than the placebo group (n=47, 5.6%). A review of death narratives did not suggest a relationship to the study drug.

Serious adverse events were not uncommon, but for those treated with denosumab (25.3% in the postmenopausal osteoporosis trials, 31.6% in the hormonal ablation therapy trials) occurred slightly more frequently than for those receiving placebo (24.3% for the postmenopausal trials, 27.6% in the hormonal ablation therapy trials). The types of serious adverse events were generally consistent for a population of advanced age and/or neoplasia, and included cardiac, musculoskeletal, infective and neoplastic disorders. Those considered possibly treatment-related were well balanced between treatment and placebo groups.

The most common reasons for discontinuation of the investigational product overall were withdrawal of consent; adverse events caused between 2% - 6.5% of all withdrawals.

Denosumab was generally associated with a mild and transient decrease in serum calcium without apparent clinical effect; in all pivotal trials and most supporting studies, supplemental calcium was given as an inclusion criterion.

Quantitative bone histomorphometry was undertaken on a relatively small fraction of the study population. The only instances of biopsies without either label occurred in patients receiving denosumab. Denosumab also altered dynamic histomorphometry parameters including activation frequency, bone formation rate per bone surface, mineral apposition rate and mineralization lag time, compared to placebo (Study 20030216) and compared to alendronate (Study 20050234). This likely reflects significant bone turnover suppression but its clinical meaning and consequence for long-term safety is unclear.

There was no evidence to suggest an increased frequency of opportunistic infections for those treated with denosumab, although serious infections were slightly more common, including skin infections (cellulitis, erysipelas); fatal adverse events of infection were well balanced between the groups.

Adjudication of potential cardiovascular adverse events was thorough in the clinical development program; there were no significant differences in the frequency of these for denosumab-treated patients compared to placebo.

Potentially treatment-related malignancies were slightly more common in the denosumab group than for placebo. In the pivotal trials of efficacy and safety in postmenopausal

osteoporosis, gastrointestinal (n=35) and female reproductive (n=21) malignancies were more common in patients treated with denosumab than placebo (n=24 and n=9 respectively). No formal carcinogenicity studies were performed during the clinical development program.

Anti-denosumab binding antibodies occurred infrequently and no neutralizing antibodies were observed during the clinical development program; there was also no evidence of increased risk of hypersensitivity or drug allergy reactions as a result of denosumab treatment.

The clinical trials included a single instance of osteonecrosis of the jaw, occurring in a patient with several other risk factors with a time course of disease that made causation by denosumab very unlikely.

Other than the expected (and not clinically significant) falls in corrected calcium, phosphorus and alkaline phosphatase, there were no significant abnormalities in serum chemistry or haematology associated with denosumab use.

Clinical Summary and Conclusions

The European Medicines Agency (EMA) has published a guideline on the evaluation of medicinal products in the treatment of primary osteoporosis; this document provides a useful framework against which to consider the sponsor's application to register denosumab in Australia.[54]

In general, the submitted studies satisfy these design requirements. The populations to be studied are appropriate for postmenopausal women in terms of estimated fracture risk and BMD T-scores, and also appear to be for men receiving hormonal ablation therapy ("men at risk of fracture" with comparably low BMD T-scores).

The efficacy measures are generally appropriate, although the evaluator notes a favouring of BMD DEXA primary efficacy endpoints, where the EMA prefer more clinically-meaningful endpoints such as new clinical fractures. Nevertheless, both endpoints were generally included in the clinical trials. The biochemical markers of bone turnover were also acceptable.

Quantitative bone histomorphometry was performed in subsets of patients in several of the Phase III trials, as the EMA requires. Other safety measures are appropriate. Acceptable active comparators (alendronate) were used in several of the supporting studies.

The EMA guidance document does specifically mention catch-up bone loss after withdrawal, and the evaluator is concerned that there is some evidence of risk of this (raised bone turnover markers in the off-treatment period of 20040132) which are unacknowledged in the existing product information and require further study.

The safety profile of denosumab appears to be generally acceptable and specific identified risks have been appropriately mentioned in the proposed product information.

Bearing the pivotal studies in mind, requirements do appear to be met to support registration for the indications of treatment of postmenopausal osteoporosis and treatment of bone loss for men with prostate cancer undergoing androgen deprivation. There is less guidance regarding registration for the indication of the treatment of bone loss in breast cancer treated with aromatase inhibitors. The proposed indication does not specify that the breast cancer be non-metastatic (as it was in the population studied in the pivotal trials). The lack of

[54] EMEA. Committee for Medicinal Products for Human Use (CHMP). Guideline on the Evaluation of Medicinal Products in the Treatment of Primary Osteoporosis. *European Medicines Agency.* [Online] 16 November 2006. [Cited: 24 August 2009.] http://www.emea.europa.eu/pdfs/human/ewp/55295enfin.pdf.

investigation into actual cancer outcomes on-treatment in this population is a concern raised recently by the FDA expert panel and shared by the evaluator. When added to a slightly increased risk of breast and female reproductive cancers in the largest pivotal trials, on balance the evaluator would not support registration for denosumab for this indication at this time.

V. Pharmacovigilance Findings

The Risk Management Plan submitted with this application was updated during the post ACPM phase and was finalised to TGA's satisfaction. See **10. Outcome**

VI. Overall Conclusion and Risk/Benefit Assessment

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

1. Quality

All chemistry and quality control issues are resolved. Denosumab is manufactured by a cell culture bioreactor process of transfected Chinese Hamster Ovary cells that produce recombinant denosumab and are harvested and purified to produce a single batch of drug substance. All viral prion safety issues have been satisfactorily addressed. Stability studies support a shelf life of 30 months at 2 to 8°C for all presentations.

The bioavailability data were not evaluated as this is not required for monoclonal antibodies.

The PSC recommended approval on quality and pharmaceutical grounds. The issues identified by PSC have been satisfactorily addressed by the sponsor. Outstanding GMP issues have been resolved.

Overall, the evaluator recommended approval from a chemistry and quality control perspective.

2. Nonclinical

The evaluator noted that the studies were generally adequate and well conducted.

In vitro studies showed that denosumab binds to human RANKL with high affinity. There was no recognition of murine RANKL; it did not bind to other human TNF family members.

Denosumab (25 mg or 50 mg SC once monthly) decreased bone resorption, increased bone mass (obvious increase of cancellous bone mass in rats), increased BMD and improved bony strength (mechanical) in a 16 month study in Cynomolgus monkeys which had been subjected to ovarian ablation. Efficacy was also seen in repeat dose toxicity studies conducted in young adult male and female monkeys where doses≥ 0.1 mg/kg SC weekly was used. There were no treatment related adverse findings. The evaluator noted that exposure achieved was 150 times the human dose proposed (based on animal: human AUC).

Specific studies to assess the potential secondary pharmacodynamic effects were not conducted. These have been assessed in the general toxicity studies and in the literature submitted. The main focus of these studies has been the effect on immune system. It was stated that no adverse effects were noted in the functioning of the immune system in Cynomolgus monkeys in the repeat dose toxicity studies at exposures≤ 150 times the clinical exposure or in the 16 month pharmacology study at exposures≤95 times the clinical exposure. No evidence of immunotoxicity was observed in monkeys in the 12 month repeat dose toxicity study (relative exposure≤ 150); in the 1 month study (relative exposure ≤ 164) in the 16 month pharmacology study.

Safety pharmacology studies in Cynomolgus monkeys did not reveal any effect on ECG, blood pressure, heart rate or respiration at doses producing 40 times clinical C_{max}. Inhibition of tooth eruption, bone growth and decreased body weight were noted in neonatal rats treated with rat OPG-Fc (surrogate of denosumab).

Systemic absorption was slow after SC injection with t_{max} being 72 hours in rodents and monkeys (c/w 1-4 weeks in humans). Linear pharmacokinetics was observed in all species; volume of distribution (Vd) was low; peak levels in target organs (that is, bone) were ≤ 12% of the serum C_{max}. Serum half lives were long in rodents, monkeys and humans (11-27 days).

No genotoxicity study or carcinogenicity study was conducted; and this was acceptable according to the ICH guideline for biotechnology derived pharmaceuticals.

There was no effect on female fertility seen in the studies on monkeys. No fertility studies on males were conducted; however, in a repeat dose toxicity study, no effect on sperm motility or histology of male reproductory tissue was seen. There was no effect on foetal weight; there was no foetal malformation when given during organogenesis. There were literature reports of failure of lymph node development and absence of lactation due to inhibition of mammary gland maturation in RANK/RANKL- knockout mice. This is addressed in the PI.

3. Clinical

3.1 Pharmacodynamics

The evaluator noted that pharmacodynamic effects were measured in pharmacokinetic studies. Urinary NTX, a biochemical marker of bone resorption was seen to decrease in a dose dependent manner when denosumab was administered at 0.01 to 3.0 mg/kg SC or IV. These changes were sustained at higher doses. Bone specific alkaline phosphatase decreased in a dose dependent manner (as would be expected). Similar findings were also seen in a study on Japanese females with breast cancer and related bone metastases, who received multiple doses of denosumab.

One study, 223, (placebo controlled) examined the dose response in terms of BMD, in 412 postmenopausal females. 6, 14 or 30 mg every 3 months or 14, 60, 100 or 210 mg every 6 months was administered. Lumbar BMD was the primary efficacy endpoint. It is stated that doses of 30 mg every 3 months and 60 mg every 6 months showed similar efficacy. This was similar to the efficacy seen with alendronate 70 mg. There was a high and sustained decrease in bone turnover markers up to 24 months. The variability was high, however. It is stated that it is a 4 year study and preliminary data on 24 months is reported. It is also stated that the dose of 60 mg 6 monthly was selected based on convenience. The sponsor was requested to provide in its pre ADEC response the summary of the findings of the primary efficacy endpoints at 4 years to confirm that 60 mg every 6 months is the minimum effective dose. The sustained suppression of bone turnover markers, that is, type 1 serum C-telopeptide (CTX1) suggests that a lower dose may have been as effective as the selected dose without the degree of suppression seen with the current dose– see safety section.

> *The sponsor responded that the 4-year data requested by the Delegate are presumably those from 4-year study 223 (which were included in the marketing application) and not from extension study 233, in which all subjects switched to*
> *60 mg every six months (Q6M) dosing and thus additional dose-ranging data are not available. In study 223, 60 mg was the lowest Q6M dose that provided maximal gains in BMD after 2 years. While both the 14 mg and 60 mg Q6M dose regimens showed evidence of reversibility in pharmacodynamic effects at the end of the dose interval (based on BTM), the*

former dose regimen provided lower BMD gains across anatomical sites. After 2 years of treatment in study 223, all denosumab-treated subjects not on 60 mg Q6M switched to either this dose regimen or placebo. Data for the 5th and 6th years of treatment with 60 mg Q6M in study 233 have shown continuous increases in BMD at lumbar spine and hip with continued acceptable benefit/risk profile.[55]

3.2 Pharmacokinetics

There were five single dose pharmacokinetic studies conducted in healthy postmenopausal women, patients with bony metastases secondary to breast cancer, multiple myeloma and females switched from alendronate therapy to denosumab. A range of doses (0.03 mg to 3.0 mg/kg) subcutaneously was used. Drug concentrations were detectable in plasma within 5 minutes to 24 hours, depending on the study. C_{max} was observed 7-14 days after drug administration and was not dose proportional. In those with breast cancer and multiple myeloma the C_{max} was more variable. This pattern was also observed in those who switched from alendronate.

Multiple dose pharmacokinetic studies used varying doses (including the dosing regimen proposed for marketing) at 4 weekly, 2, 3 and 6 monthly intervals. The evaluator noted that pharmacokinetics did not vary significantly to that observed with single dose studies.

Non linear kinetics was observed in the single and multiple dose studies. The bioavailability of the subcutaneous doses ranged from 35% to 78%. The Vd was in the range of 28.9 mL/kg to 54.5mL/kg. The evaluator noted that this is similar to that of total body water and it is likely that denosumab is not widely distributed outside the vasculature. Metabolism is unlikely to involve hepatic pathways. Elimination takes place slowly from plasma. The elimination half life increased with dose, both via the intravenous and subcutaneous route. The mean half life following SC route at 0.03mg/kg and 3mg/kg were 23.3 days and 29.5 days. Similarly clearance decreased with dose: at 0.03 mg/kg SC the mean apparent clearance was 0.520 ± 0.403 mL/h/kg and at 3.0 mg/kg was 0.0634 ± 0.403 mL/h/kg. Effects of hepatic impairment were not evaluated.

One study examined the pharmacokinetics of denosumab given as a single SC dose of 60 mg of denosumab in several groups of patients with varying degree of renal impairment. There appeared to be no effect in pharmacokinetics. The evaluator also stated that effect on age and sex were not seen; (though this was not directly studied, cross study comparisons and population pharmacokinetics suggested no variation).

There was a population pharmacokinetic analysis based on the 14 clinical studies (6 Phase 1 studies, 5 Phase II studies and 3 Phase III studies). The evaluator concludes the following: "a two-compartment open model with first order absorption, parallel linear and capacity-limited elimination best characterized denosumab pharmacokinetics by population kinetic modelling. The pharmacokinetic impact of body weight, patient population and race is predicted to be limited using the population kinetic model"**.**

3.3 Efficacy

3.3.1 Treatment of osteoporosis: There was one pivotal study addressing the proposed indication and several supportive studies.

[55] Miller P, Bolognese M, Lewiecki E et al. Effects of Denosumab on Bone Mineral Density and Biochemical Markers of Bone Turnover: 6 Year Results of a Phase 2 Clinical Trial. ASBMR 31st Annual Meeting 2009; Denver. Abstract 1026.

The pivotal study was a Phase III multicentre double blind placebo controlled study where subjects were randomised on a 1:1 ratio to receive denosumab at 60 mg SC versus (placebo) every 6 months for three years. All enrolled patients had a lateral spine X-ray and DEXA at screening, 12, 24 and 36 months (or termination, if earlier). In addition to the main study, patients were invited in some study sites to participate in 7 protocol described sub studies (including a fracture healing substudy, bone biopsy substudy and bone marker substudy).

The primary efficacy measure was the incidence of new vertebral fractures during the entire 36 month period. This was determined by a pair of independent blinded radiologists using a validated semi-quantitative method. The secondary efficacy endpoints were time to first nonvertebral fracture and time to first hip fracture.

The evaluator noted that the study was designed to provide at least 99% power to detect a 45% difference on the primary endpoint using χ^2 tests of equal proportions at 36 months (∞=0.05). Analyses were carried out in ITT and per protocol populations.

The ITT population was 7,808 patients; 3902 received denosumab and 3906 received placebo. Mean age was 72.3 years ± 5.2. The baseline BMD, fracture history, calculated fracture history according to the validated WHO risk estimating FRAX algorithm were evenly balanced between the two groups (53% has previous history of any fracture). The evaluator noted that there was no significant difference in subject disposition between groups; it is reported that 83% completed the trial. The percentage of withdrawals was similar and the reasons also similar between groups.

The crude incidence of new vertebral fractures were (placebo versus denosumab) 2.2 % versus 0.9% in 0-12 months; 3.1 versus 0.7% in 12-24 months; 3.1 versus 1.1 % in 24 to 36 months (Table 6). Though these figures are small, there appears to be a trend to a small increase in the third year in comparison to the second. The crude incidence of non vertebral fractures (including hip fractures) at different time points could not be found in the submission. The sponsor was requested to submit this in its pre–ADEC response in order to ascertain whether there is a slight reduction in effect in relation to non vertebral fractures by the third year.

> *The sponsor responded that for the 30 clinical studies submitted in the marketing application, only the pivotal PMO trial (study 216) and the pivotal prostate cancer HALT trial (study 138) were powered or designed to assess fracture efficacy. Study 141 and 234 were powered to assess BMD. In these studies, fractures were collected as adverse events and relied on spontaneous reporting by patients and doctors. Reports of fractures were not systematically confirmed by X-ray. Furthermore, lateral spine X-rays were not obtained to evaluate the incidence of vertebral fracture, the most common and typical osteoporotic fracture.*

Secondary endpoints are shown in Figures 4 and 5. Denosumab significantly decreased the incidence (based on Kaplan Meier estimates) of non vertebral fractures (secondary endpoint) from 8% in the placebo group to 6.5% (HR: 0.8, p=0.0106) and of hip fractures (secondary endpoint) from 1.2% in the placebo group to 0.7% (HR: 0.60, p=.03).

Tertiary endpoints included BMD at various sites. There were statistically significant results at various sites favouring denosumab over placebo. There were several sub studies conducted including bone biopsy which is discussed under safety. Bone marker substudy on 160 patients showed significant suppression which was rapid and lasting.

3.3.2 Supportive studies

All these studies used BMD as the primary endpoint and hence, are considered supportive data only.

One study, 132, assessed the efficacy of denosumab in preventing lumbar bone loss in postmenopausal osteopenia with lumbar BMD minus 1.0 to minus 2.5. Since this indication is not sought by the sponsor, it is considered only a supportive study. The study was double blind randomised placebo controlled with denosumab 60 mg administered 6 monthly (or placebo) SC for 18 months. 332 patients were enrolled with 166 receiving denosumab and 166 receiving placebo. There was a statistically significant increase in BMD in denosumab (6.2%) versus (-1.2% in placebo $p<0.001$). There was statistically significant difference favouring denosumab over placebo at several other BMD sites and in relation to indices of bone turnover.

The second study, 141 (a double blind randomised multicentre study) compared denosumab 60 mg 6 monthly versus 70 mg alendronate weekly. This was a 12 month study. 593 patients received denosumab and 586 received alendronate. This was a non-inferiority study which was then tested for superiority. The evaluator noted that there was superiority of denosumab over alendronate in terms of lumbar spine, femoral neck, total hip, trochanter and distal radius BMD. However, it is stated that fractures were reported in 18 patients (3%) who received denosumab versus 13 patients who received alendronate (2%). The evaluator noted that statistical significance was not reported relating to this end point.

There was one other study (234**),** which assessed subjects on alendronate who were then switched to denosumab. 504 women with lumbar spine or total hip BMD T score between minus 2.0 and minus 4.0 were either given 70 mg alendronate weekly or denosumab 60 mg SC every 6 months. Treatment was continued for 12 months. There was superiority seen (after establishing non-inferiority) with denosumab in relation to BMD. There was a significantly greater decrease in sCTX1 compared with alendronate. No fracture incidence is mentioned. The sponsor was requested to state whether there were reports of fracture and whether they were actively sought. The findings should be submitted in its pre-ADEC response. *The sponsor's response on the issue of fractures has been included above.*

Two studies with interim analyses did not add any relevant information to this submission.

3.3.3 Treatment of bone loss in hormonal ablation:

In women with non-metastatic breast cancer receiving aromatase inhibitor therapy

Pivotal study 135 was a phase III randomised double blind placebo controlled trial of efficacy and safety of denosumab in treating bone loss in women with non metastatic breast cancer with low bone mass (lumbar BMD minus 1.0 to minus 2.5) who were receiving aromatase inhibitor therapy. Patients were randomised on a 1:1 basis to receive denosumab 60 mg SC (or placebo) every 6 months for 18 months. There was a follow up visit scheduled at 24 months. Subjects received calcium (1 g) and vitamin D (400 IU) daily as general standard of care for bone loss. DEXA at radius, lumbar spine, femoral neck and total body were conducted at regular intervals. Inclusion criteria were female 18 years and older with histologically and cytologically confirmed early stage, oestrogen receptor positive adenocarcinoma of the breast. They were to be free of distant metastasis.

A total of 252 patients were enrolled of whom 127 were randomised to denosumab and 125 to placebo. The mean age was 59.5 ± 9.3 years. The baseline demographics and BMD T scores were similar between groups. The evaluator noted that sample size calculations were adequate to detect a difference of 2 percentage points in lumbar BMD at 12 months.

The primary efficacy endpoint was the change in lumbar BMD from baseline to Month 12. This was statistically significant for denosumab: 4.8% for denosumab (95% CI of 4.3% to 5.4%); compared with placebo -0.7% (95% CI of minus 1.3% to -.1%). Secondary efficacy endpoints included BMD at femoral neck and total hip. These were statistically significantly superior in denosumab compared with placebo. The evaluator also noted that sCTX1 (a bone turnover marker) exhibited a rapid, sustained and significant decrease in the denosumab group compared with placebo.

In men with non-metastatic prostate cancer with hormone deprivation therapy

Study 138 was similar in design to the previous study and was conducted on men with non-metastatic prostate cancer treated with hormone deprivation therapy; this was a 36 month study.

Men < than 70 years of age who had histologically confirmed prostate cancer and a history of osteoporotic fracture or a BMD T score at the lumbar spine, total hip or femoral neck of <minus 1.0. Men over the age of 70 did not have to meet the latter requirements. All subjects were required to have undergone bilateral orchidectomy or initiated ADT (androgen deprivation therapy) with gonadotrophin releasing hormone agonist and have no exposure to bisphosphonates or other medications known to affect bone metabolism.

A total of 1468 patients were enrolled: 734 were randomised to receive denosumab and 734 on placebo. The subjects were stratified according age≤ 70 or > 70 years. The primary efficacy endpoint at 24 months showed a statistically significant increase in BMD in lumbar spine: the mean percentage change from baseline was 5.6% in denosumab group versus minus 1.0%. This effect was seen in both strata.

Other BMD (which were secondary endpoints) measures were also significant at 24 and at 36 months.

The incidence of new fractures at 36 months, which was also a secondary efficacy endpoint, showed the following:

	Crude Incidence		Risk Comparison Estimates						
			Absolute Risk Reduction (%)[a]		Risk Ratio[a]		Odds Ratio[b]		
	n/N1	%	Pt Est	(95% CI)	Pt Est	(95% CI)	Pt Est	(95% CI)	p-value
Placebo (N = 734)	26/673	3.9							
Denosumab 60 mg Q6M (N = 734)	10/679	1.5	2.4	(0.7, 4.1)	0.38	(0.19, 0.78)	0.37	(0.18, 0.78)	0.0063

However difference in time to first clinical fracture was not statistically significant.

3.3.4 Long term efficacy results:

Study 216 was of three years duration. There was sustained efficacy relating to the primary efficacy endpoint, bone turnover markers. There was an extension study of 223 that was of 4 years duration. This study is stated to have shown a sustained efficacy in terms of lumbar BMD and urinary bone turnover markers.

3.3.4.1 Effects of discontinuation of denosumab

BMD and bone turnover markers: In study 132, the subset (n=128) that was followed up showed that BMD had decreased but did not reach baseline levels by Month 36 (that is, 12 months off treatment). In this study, the findings at the end of the extension phase are not given. This was requested to be submitted in the sponsor's pre-ADEC response. Similarly, in studies 223 and 144, BMD returned to baseline in 12 months off treatment; bone turnover markers returned to baseline levels in 24 months.

> *The sponsor responded that three studies evaluated the effects of discontinuing denosumab on BMD (study 223, 144 and 132) and bone turnover markers (223 and 132). Final results from study 132 were provided. Increases in BMD and decreases in bone turnover markers observed with denosumab treatment were reversible. BMD generally returned to pre-treatment levels at all measured sites (but remained above levels in the placebo group), indicating that the magnitude of the reduction in BMD following discontinuation of denosumab treatment was similar to the level of increase in BMD during treatment. Levels of bone turnover markers increased to values above baseline and greater than those of the placebo group with discontinuation of denosumab treatment. However, after 24 months without treatment (Month 48), levels of sCTX1 and P1NP had returned to values near baseline. Bone remodelling remained coupled after treatment was discontinued. To further evaluate effects of therapy discontinuation, two studies in women with low bone mass or osteoporosis are ongoing to address changes in microstructure by high resolution-peripheral and changes in remodelling at the tissue level by histomorphometry after discontinuation of denosumab treatment. The sponsor committed to providing the final clinical study report.*

Fractures: This is not provided. However, in the US public discussion document it is mentioned that after discontinuation, in the breast cancer study, "there were twice as many fractures" in the denosumab group compared with placebo. The sponsor should provide the summary of these findings.

3.3.4.2 Effects of retreatment after withdrawal:

The evaluator noted this in relation to study 233. Safety results were available for 31 subjects retreated with denosumab. No undue safety concern was identified in this small group.

4. Efficacy Summary

The Delegate summarised efficacy with regard to the proposed Indications as follows:

4.1 Treatment of osteoporosis in postmenopausal women. Prolia significantly reduces the risk of vertebral, non-vertebral and hip fractures:

The pivotal study (216) provides evidence of efficacy of denosumab in the treatment of osteoporosis in postmenopausal women with osteoporosis as defined by a BMD T score of less than minus 2.5 at the lumbar spine, hip or both. Fracture reduction is provided for three years only and thus should be recommended for this duration alone. This is because safety of long term use is not provided. In addition, there appears to be a slight tapering of effect in terms of vertebral fractures in the last 12 months; the significance of this can only be ascertained by reviewing the findings in relation to non-vertebral and hip fracture data during the same time period. The sponsor should submit the number of fractures and the crude incidence for these categories in the pre-ADEC response.

With cessation of treatment the BMD reduces to baseline levels by 12 months. No data were provided on fracture incidence after cessation of therapy.

There are no adequate data to recommend re-treatment.

Switching from bisphosphonates to denosumab is also not currently recommended as the data are preliminary. Bone biopsy samples showed significant suppression in this subset and thus this is not recommended at present.

These limitations should be included in the Clinical Trials section in the PI.

4.2 Treatment of bone loss associated with hormone ablation

The study 135, on 252 women with non-metastatic breast cancer showed increase in BMD in lumbar spines, femoral neck and hip (at 12 months). It was questioned if this correlate to a decrease in fracture reduction or to reduction in cancer morbidity. These have not been shown and the "at risk" population has not been targeted in this study. Similarly, the study on prostate cancer patients recruited some patients with normal BMD and showed BMD preservation and reduction in new fractures. This is a large heterogeneous population, the study has not targeted those at risk of fractures or linked these findings to overall better outcomes in relation to cancer morbidity. Thus, efficacy data are not convincing.

5. Safety

The evaluator noted that a total of 7800 patients were exposed to denosumab in the submitted studies (approximately 13, 000 patient years of exposure). The evaluator has discussed the individual study results and concludes that denosumab was "generally well tolerated". There were no significant difference in common adverse events (compared with placebo). It was stated that serious adverse events occurred "slightly more commonly with denosumab"; however, treatment related AEs were similar.

The evaluator also noted that "potentially-treatment-related malignancies were slightly more common in the denosumab group than for placebo. In the pivotal trials of efficacy and safety in postmenopausal osteoporosis, gastrointestinal (n=35) and female reproductive (n=21) malignancies were more common in patients treated with denosumab than placebo (n=24 and n=9 respectively). No formal carcinogenicity studies were performed during the clinical development program".

There was a mild transient decrease in serum calcium; all studies used supplementation with calcium and Vitamin D.

The Delegate noted the following:

Infection: There appears to be an increase in infection relating to skin, urinary tract and endocardium. There were 3% of denosumab patients who were hospitalised with infection in study 223. In study 132, 8 (4.9%) subjects on denosumab had "serious infection" versus 1 (0.6%) in placebo; similarly, in study 216, there were 4.1% in denosumab versus 3.4% in placebo; of these, erysipelas and cellulitis accounted for 13 reports in the denosumab group versus 1 in the placebo group. There were 16 reports of urinary tract infection versus 10 in placebo. There were also 3 cases of endocarditis in denosumab (where one died and one received valve replacement); there were none in the placebo group. It is also stated that serious AEs $\geq$ 0.2% difference between groups was seen (5.9%) in denosumab than in placebo (4.6%) in study 138. There were 8 reports of septic arthritis in study 216, which were classified as non serious and requiring oral antibiotics. This may have been a wrong coding of the event and the sponsor was requested to clarify how septic arthritis was classified as non-serious.

The sponsor responded that verbatim adverse events terms indicated an infection at or in a joint and were mapped to the MedDRA term preferred term of infective arthritis. Clinical review confirmed that all cases were reported as mild to moderate in severity and all subjects remained on denosumab treatment with no recurrent infections reported with subsequent doses. Blood cultures, or reports of aspiration of joints and culture results, were generally not available. Systemic symptoms of infection were not reported. Preceding events reported in individual subjects included a thorn cut leading to cellulitis, a concurrent adverse event of skin ulcer and a non-serious post-operative infection while hospitalised for knee surgery. Based on the clinical presentations and the limited information provided in these cases it appears that using clinical judgement, the investigator considered that these events did not meet criteria for serious adverse events.

Malignancy: There were three malignancies reported in the dose finding study, 223. This was reported in the high dose (100 mg 6 monthly group of a total of 41 subjects). In the pivotal PMO study 4.3% (n=166) reported malignancy in placebo versus 4.8% (n=187) in denosumab group. The imbalance of greater than 0.2% was seen in relation to breast (34 versus 26), reproductory organs and gastrointestinal malignancies. It was noted in the FDA Public discussion that in study 135 the metastatic events were 7% versus 4.2% (denosumab versus placebo). Similarly, in study 138 metastatic events were 8.2% versus 5.5% (denosumab versus placebo).The latter two studies were conducted in patients with breast cancer or prostate cancer.

Dermatological events: In the PMO studies the incidence of AE within skin and subcutaneous tissue were 15.1% denosumab and 12.4% placebo. Eczema was 3.1% versus 1.7% placebo.

Pancreatitis: The evaluator also reported that episodes of pancreatitis (in pivotal studies) appeared to be more common in the denosumab group (9 events in 8 patients) compared to placebo (4 events in 4 patients). In two cases, both treated with denosumab, the episodes of pancreatitis led to death.

Cataract: In study 138 1.2% in placebo and 4.7% in the denosumab treated group. This was not seen in other studies. There is currently a multicentre double blind placebo controlled study that is being conducted on similar patient group; the objective is to ensure that the incidence is not statistically significantly different to placebo.

Decreased serum calcium: One denosumab treated subject in study 138 reported a serious event of decreased calcium. In the PMO studies asymptomatic corrected calcium level < 8.5mg/dL was 1.6%. It was questioned if there was secondary hyperparathyroidism that was causing a compensatory increase in serum calcium? The sponsor was requested to submit in its pre-ADEC response the incidence of increased PTH in denosumab group versus placebo.

The sponsor responded that following administration of denosumab, there were mild, transient, compensatory increases in iPTH as a consequence of the mild, transient decreases in serum calcium. During the 30 clinical studies in patients treated with denosumab plasma calcium levels were stable, including study 138; in study 216 there were only 3 cases of clinical hypocalcaemia which only occurred in the placebo group. An iPTH increase after each injection of denosumab is a favourable response as this occurs at a time when most osteoclasts are suppressed by the recent denosumab injection; this favourable pattern is a clinically desirable effect for an anti-

osteoporotic drug. Changes in iPTH were not associated with any clinical or safety findings, and there was no evidence of sustained or persistent/ autonomous hyperparathyroidism.

Osteonecrosis of the Jaw (ONJ): No cases were seen in the completed studies. However an investigator's brochure for a Clinical Trial Number 2009/453 states one report in a patient with prostate cancer who has no previous treatment with bisphosphonate therapy. The sponsor was requested to state if there were any additional reported cases in ongoing studies in its pre-ADEC response.

The sponsor responded that there have been no positively adjudicated cases of ONJ in any completed or ongoing denosumab study using a dosing regimen of 60 mg Q6M in the PMO and HALT settings. Results from the primary analysis of 2 phase 3 studies in patients with advanced cancer receiving 120 mg denosumab SC Q4W or 4 mg IV zoledronic acid showed that the incidence of ONJ was balanced between treatment groups, with most subjects having the recognised clinical risk factors for ONJ (2.0% denosumab, 1.4% zoledronic acid in breast cancer study 20050136, p = 0.3876 and 1.1% denosumab, 1.3% zoledronic acid in advanced cancer/multiple myeloma study 20050244, p = 1.0). The occurrence of ONJ in the advanced cancer population treated with denosumab has been included and clarified in the draft PI. The findings observed in the advanced cancer study cannot be translated to osteoporosis setting because other risk factors in the cancer setting influence events of ONJ.[56] *In addition, the dose of denosumab in the advanced cancer was approximately 12 times higher (120 mg every 4 weeks) than in the osteoporosis setting (60 mg Q6M), with a different pharmacokinetic and pharmacodynamic profile.*

Immune response: A total of 29 patients treated with denosumab and 14 treated with placebo tested positively for anti-denosumab binding antibodies. None were neutralizing and no association with an alteration to the drug's safety or efficacy was noted. The implication of this is not clear.

Bone biopsy abnormalities: The evaluator noted the findings of the biopsy results of the substudy in 216. However, bone biopsies were available from studies 216**,** 234 and 223. 218 biopsies were evaluable for histomorphometry in 198 subjects. The following details were obtained from the FDA public discussion and the submission:

Five subjects in study 216 did not have osteoid that could be seen at Month 24. Osteoid is new unmineralised bone matrix; and lack of osteoid may indicate bone suppression. One subject at Month 36 showed endosteal resorption of cortical bone which can be associated with reduced bone strength. One subject maintained on alendronate in Study 234 had evidence of marrow fibrosis. Tetracycline courses were given to label bone. Labelled tetracycline provides evidence of active bone remodelling and formation. No label was present in 20% at Month 12 in study 234 and in 216, 35% had no label at Month 24 and 38% at Month 36. It was stated in the sponsor's *Clinical Summary* that the findings were consistent with reduction in bone remodelling in subjects treated with denosumab compared with placebo or alendronate: at Month 24 and 36 (in study 216) parameters of bone resorption were significantly suppressed. In some biopsy samples it was virtually absent. Those on

[56] Reid I. Perspective: is bisphosphonate-associated osteonecrosis of the jaw caused by soft tissue toxicity? Bone 2007;41:318-320.

alendronate who switched to denosumab also showed significant suppression, this appeared to be correlated to the significant suppression of bone turnover marker CTX1 which also showed sustained suppression.

The Delegate's concerns were that the findings in relation to infections may be a signal of defective immune response; similarly the increase in malignancies (though small) may be also due to defective immune responses. There is also a signal of significant and sustained bone suppression; the long term implications are not clear.

6. Evaluator's recommendation

Based on the data submitted the evaluator recommended approval of denosumab in the treatment of osteoporosis and in the treatment of bone loss associated with hormone ablation in men with prostate cancer.

The evaluator was against registration of denosumab for the treatment of bone loss in women with breast cancer as cancer outcomes are not factored in the analysis; and because there was a slight increase in risk in breast and reproductory organ malignancies in the denosumab treated groups in the large pivotal studies.

7. Risk-Benefit Analysis

7.1 Delegate's Analysis

Minimum effective dose: This has not been clearly identified in dose selection studies. It appears that a smaller dose may have been just as adequate based on BMD, bone turnovers etc.

Treatment of osteoporosis: There is one large double blind study that shows that denosumab is effective in the treatment of osteoporosis in postmenopausal women. However, the duration of treatment at this stage should be limited to three years. Osteoporosis criteria used in the pivotal study should be included in the Indications section as a prerequisite for treatment with denosumab.

There is a concern that the effect plateaus at (or before) three years in relation to hip fractures. It was not known if this indicates a reduction in efficacy. This requires monitoring with analysis of ongoing studies when completed. This must be a condition of registration.

It was not possible to ascertain if there is over suppression of bone turnover with available data.

There are safety concerns. The main concerns based on the present dataset are that of defective immune response and malignancy. The increased incidence of infections in the denosumab group may be a signal of defective immune response; similarly, the increased metastatic events in the studies in prostate cancer and breast cancer subjects also suggest impaired immunity. Thus, if there are patient registries proposed in other countries, this should be extended to include Australian patients as well. The sponsor indicated that the Scandinavian database that will operate the EU patient registry will not be accessible to Australian prescribers and/or patients.

The studies that are ongoing should be submitted upon completion to ascertain risks relating to suppression of bone turnover, infections and other safety issues identified. These findings also should be included in the Precautions section of the PI till further data are provided to downgrade them.

A lifetime limit of 3 years treatment is reasonable, unless the advisory committee recommends 2.5 years.

All Phase IV commitments to other regulatory agencies were requested to be notified to the TGA in the sponsor's pre-ADEC response. *The sponsor provided a list of Phase IV commitments.*

The studies, on completion, should be submitted to the TGA for evaluation.

In terms of preservation of BMD in the cancer population, there were two pivotal studies submitted. Study 138 was a large study that showed bone preservation up to Month 36 (dosed 6 monthly to Month 30) in prostate cancer patients. There was statistically significant reduction in vertebral fractures seen at 36 months. Unfortunately, this and the study on breast cancer patients (study 135) did not identify the "at risk" population; nor were the studies designed to show any improvements in cancer outcomes.

There are safety concerns identified in this patient group. There was an excess of metastatic events in the denosumab treated group in both studies. There is also a report of higher fracture incidence in the denosumab group in the breast cancer study on discontinuation. These concerns need to be allayed with more data if the sponsor wish to pursue these indications. At present the available data preclude the registration of denosumab for these indications as the risk outweighs the benefit.

The Delegate proposed to register denosumab 60 mg/mL (Prolia) for the treatment of osteoporosis in postmenopausal women. Prolia significantly reduces the risk of vertebral, non-vertebral and hip fractures.

The Delegate proposed to reject denosumab 60 mg/mL (Prolia) for the treatment of bone loss associated with hormone ablation in men with non-metastatic prostate cancer and in women with non-metastatic breast cancer due to inadequate evidence of efficacy and safety.

8 Sponsor's Response

The sponsor responded to the Delegate's overview. It disagreed with the Delegate's recommendation to limit the use of denosumab in the treatment of post menopausal osteoporosis (PMO) to 2.5 to 3 years.

> *The sponsor responded: First, the clinical program meets regulatory requirements in Australia for the chronic use of denosumab in the treatment of post-menopausal osteoporosis. The clinical evaluator did not propose restrictions for the duration of denosumab use and no such limitation will apply in the EU. The scope of safety data included in the registration application surpasses the ICH exposure requirements and supports chronic use of denosumab with no limitation on treatment duration in accordance with the EMEA CHMP Guideline for the Evaluation of Medicinal Products for the Treatment of Primary Osteoporosis (CPMP/EWP/552/95 Rev2) as adopted by TGA.*
>
> *Second, no additional safety concerns have been observed with long-term denosumab treatment. Data collected from the 4-year parent phase (study 223) and the 2-year extension phase (study 233), demonstrate that denosumab "is effective and well tolerated through 6 years continuous treatment".*[53] *In addition, the sponsor has committed to a comprehensive pharmacovigilance program, which includes a post-marketing safety observational study leveraging data from several large medical claims databases and long-term safety (up to 10 years) in 4550 subjects (study 289, an open-label extension study for subjects from the pivotal PMO study 216).*

Third, there is no evidence of loss of denosumab efficacy with chronic treatment. The efficacy of denosumab over time for new vertebral, non vertebral and hip fractures was shown throughout study 216 without evidence of tapering of effect by year 3. Study 216 was designed to assess cumulative treatment effect at 3 years; therefore, assessments of earlier time points, or yearly rates, were underpowered.

Regarding the incidence of new vertebral fractures, the sponsor did not agree with the Delegate's suggestion of "a slight tapering of effect in terms of vertebral fractures at the last 12 months".

The sponsor responded that denosumab demonstrated efficacy for the reduction in the annual incidence of new vertebral fractures within years 1, 2 and 3 of the study with consistent and similar risk reductions of 61% (95% CI: 42 to 74; p < 0.0001), 78% (66 to 86; p < 0.0001) and 65% (49 to 76; p < 0.0001), respectively. By-year incidences of new vertebral fractures were consistent in both the denosumab group (0.9%, 0.7% and 1.1% for years 1, 2 and 3) and the placebo group (2.2%, 3.1% and 3.1%, respectively). The incidence of non vertebral fracture and hip fracture were consistent over time in the denosumab group (non vertebral fracture: 2.5%, 2.0% and 2.1% for years 1, 2 and 3; hip fracture: 0.3%, <0.1% and 0.3%, respectively). By contrast, the incidences in the placebo group decreased over time (non vertebral fracture: 3.0%, 2.8% and 2.4% for years 1, 2 and 3; hip fracture: 0.5%, 0.4% and 0.3%, respectively). The analysis for the non vertebral (p = 0.6398) and hip fracture (p = 0.1524) indicated that there was no evidence that the treatment effect varied with time. As a result, Amgen considers that the efficacy of denosumab over time for non vertebral and hip fracture is consistent, without evidence of tapering of effect over 3 years.

The sponsor disagreed with the Delegate's recommendation to limit the use of denosumab in the treatment of PMO to bisphosphonate (BP) naïve patients.

The sponsor responded that: As stated above, the denosumab clinical program meets regulatory requirements in Australia for the use of denosumab in the treatment of PMO, without restriction to BP naïve patients. No studies examining the safety and efficacy of osteoporosis therapies after switching from one therapy to another have been required as a condition of registration for approved osteoporosis therapies in Australia. In addition, there are no restrictions in the approved product information for other osteoporosis therapies regarding switching therapies.

Although not required for registration, Amgen performed Study 234 (a randomised, double-blind, active-controlled, double-dummy, parallel-group study in 504 women with post-menopausal osteoporosis) to provide information on the safety and efficacy of switching from BP therapy to denosumab.[57] *The safety profile was similar for subjects transitioning from alendronate to denosumab and those continuing on alendronate therapy, including the overall incidence of treatment-emergent adverse events, serious adverse events and treatment-related adverse events. The bone biopsy data from study 234 showed normal bone histology and reductions in bone*

[57] Kendler D, Roux C, Benhamou C, et al. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women transitioning from alendronate therapy. J Bone Min Res, Posted online 13 July 2009.

turnover consistent with the mechanism of action of denosumab.[58] In addition, pre clinical studies in monkeys showed that transition from high-dose alendronate to high-dose denosumab had no negative influence on bone quality or strength.[59]

Published studies have not reported safety issues when subjects were switched between osteoporosis therapies, including changing from one type of anti-resorptive to another within the same class. For example, alendronate to zoledronic acid (changing anti-resorptive therapy to a different class), alendronate to raloxifene or alendronate or raloxifene to teriparitide (changing from an anti-resorptive therapy to an anabolic therapy).[60,61,62] Similarly, the safety of transitioning from long-term alendronate treatment to denosumab was established in study 234. The sponsor was not aware of any existing clinical guidelines that provide guidance for changing osteoporosis therapies, particularly among anti-resorptive treatments, and considers that the decision to switch osteoporosis therapies should be made by the treating physician. Data from the ongoing trial (study 20060232) will provide information on bone turnover markers (BTM) and bone mineral density (BMD) effects after switching from denosumab to alendronate in approximately 125 subjects; the sponsor committed to providing the final clinical study report for this study.

The sponsor stated it had elected to defer consideration in Australia of the component of the marketing application for the treatment of bone loss associated with hormone ablation in women with non metastatic breast cancer (study 135 – HALT setting). It disagreed with the Delegate's statement that there is inadequate evidence of the efficacy and safety of denosumab in the breast cancer HALT population. The sponsor stated the design of study 135 was predicated on bridging fracture efficacy from women with PMO (study 216), provided similar gains in BMD were demonstrated in both studies, since the patient populations and aetiology of bone loss (due to oestrogen deprivation) were similar in each population. Since study 216 did demonstrate fracture efficacy and both studies demonstrated similar gains in BMD with denosumab therapy, efficacy has therefore been demonstrated in the breast cancer HALT population. In addition, no unique safety findings were observed in this population. The sponsor recognised that the bridging principle has not been acknowledged by the TGA clinical evaluator or the Delegate.

The sponsor disagreed with the Delegate's proposal to reject denosumab for the treatment of bone loss associated with hormone ablation in men with prostate cancer due to inadequate evidence of efficacy and safety. The sponsor responded that:

[58] Reid I, Benhamou C, Bolognese M et al. Effects of denosumab on bone histology and histomorphometry: the FREEDOM and STAND studies. 31st Annual Meeting of the American Society of Bone and Mineral Research; Denver, Colorado, USA. 2009.

[59] Ominsky MS, Smith SY, Vlasseros F, Samadfam R, Kostenuik PJ. Transition from alendronate to denosumab in ovariectomized cynomolgus monkeys maintained or improved cortical and trabecular bone mass, without altering the linear relationship between bone mass and bone strength. ASBMR 30th Annual Meeting 2008; Montreal. Abstract 1072.

[60] McClung M, Recker R Miller P et al. Intravenous zoledronic acid 5mg in the treatment of postmenopausal women with low bone density previously treated with alendronate. Bone 2007;41:122-128.

[61] Michalska D, Stepan JJ, Basson BR, Pavo I. The effect of raloxifene after discontinuation of long-term alendronate treatment of postmenopausal osteoporosis. J Clin Endocrinol Metabol 2006;91:870-877.

[62] Ettinger B, San Martin J, Crans G, Pavo I. Differential effects of teriparatide on BMD after treatment with raloxifene or alendronate. J Bone Min Res 2004;19:745-751.

Study 138 is the first demonstration of anti-fracture efficacy with anti-osteoporotic therapy in non metastatic prostate cancer patients at increased risk of fracture. The Delegate has described the study population for study 138 as "heterogeneous" and "has not targeted those at risk of fractures or linked these findings to overall better cancer outcomes in relation to cancer morbidity. Thus efficacy is not convincing".

In study 138, treatment with denosumab statistically significantly increased BMD relative to placebo, as assessed by dual-energy X-ray absoptiometry (DXA), at the lumbar spine, total hip, and femoral neck at Month 24 and Month 36 (adjusted p <0.0001). The mean change in lumbar spine BMD at Month 24 (the primary endpoint) was 5.6% in the denosumab group compared with minus 1.0% in the placebo group, a statistically and clinically significant difference of 6.7% (95% CI: 6.2, 7.1) (adjusted p < 0.0001). Denosumab also significantly reduced the risk of new vertebral fractures relative to placebo through Month 36 by 62% (relative risk, 0.38; 95% CI, 0.19 to 0.78; adjusted p = 0.0125; unadjusted p = 0.0063). The fracture benefits were demonstrated in the entire study 138 population, thereby supporting that patients with these characteristics are at increased risk for fracture. Therefore, the sponsor maintained that all patients had increased risk of fracture in study 138 and that efficacy has been demonstrated in the HALT prostate population.

Furthermore, the proposed prostate HALT indication in Australia is consistent with the "CHMP positive opinion" for the prostate HALT indication in the EU as the sponsor has ***added a clarification*** *to the indication in the draft PI that reads:*

"The treatment of bone loss associated with hormone ablation in men with prostate cancer ***at increased risk of fracture****. Prolia significantly reduces the risk of vertebral fractures."*

Study 138 was not designed to evaluate whether cancer outcomes improved with denosumab therapy, but rather to evaluate the percentage change in BMD and anti-fracture efficacy. Regardless, because this population had underlying cancer, several pre-specified analyses were conducted to evaluate cancer outcomes, including analysis of changes in prostate specific antigen (PSA), end-of-study bone scintigraphy, and overall survival. Objective comparative assessments of these outcomes and evaluation against prevalence rates in age- and sex-matched populations provide no evidence that denosumab increases the risk of progression of pre-existing malignancy in this population. Finally, denosumab was well-tolerated in men with prostate cancer, with no unique safety findings compared to women with PMO, other than an increased incidence of cataracts reported as adverse events. This adverse effect is acknowledged in the draft PI and CMI. There is no biologically plausible mechanism associating RANKL inhibition with development of cataracts; however, and as noted by the Delegate, the sponsor has initiated the two year, prospective, randomised, placebo-controlled study (Protocol 20050560) to evaluate new or worsening lens opacifications in the non-metastatic prostate cancer HALT setting.

The Delegate raised concerns regarding "infections", "malignancies", "metastatic events" and there "may be a signal of defective immune response":

> *The sponsor responded that Amgen has reviewed the available nonclinical data and the available scientific literature for denosumab or RANKL inhibition for evidence of effects on the immune system and the potential for immune system dysregulation. Evaluated as a whole, the available data demonstrate no overt effects of denosumab on immune system function, and no evidence that RANKL inhibition should increase the risk of malignancy or infection in denosumab-treated adults.*
>
> *A greater incidence of serious adverse events of skin infections was observed in the placebo-controlled PMO study 216; however, in the majority of the 30 clinical studies conducted with denosumab, the incidence of skin infections was balanced between the drug-treated and comparator groups. Under the Adverse Effects section of the draft PI, the increased rate of skin infections that lead to hospitalisation following treatment with denosumab in PMO is described (0.4% denosumab, 16 of 4,050; 0.1% placebo, 3 of 4,041). In most instances of skin infections leading to hospitalisation, the clinical course was uncomplicated, required a single course of antibiotic(s) and no recurrent infections occurred. Conditions associated with an impaired immune system may be manifested as cell-mediated immune deficiency including opportunistic fungal, viral and parasitic infections. In the denosumab clinical program, no increased incidence in such infections has been observed with long-term denosumab usage. Therefore these data indicate that denosumab is not broadly immunosuppressive. In addition, a subgroup analysis in denosumab-treated subjects who could possibly have an impaired immune system, such as those receiving concurrent steroids and subjects of older age (≥ 75 years), demonstrated a similar pattern of infection adverse events and serious adverse events as the overall study population.*
>
> *Malignancy of immune suppression has a well recognised pattern (for example, non-Hodgkin's lymphoma and oncovirus-associated malignancies), no trend for such cancers indicative of impairment of host response or cellular immunity has been observed in the 30 clinical studies evaluated for the denosumab marketing application, including both healthy and immune-compromised populations.*
>
> *Pre clinical evidence suggests that denosumab does not pose a risk of malignancies or disease progression. In the clinical program, malignancies were balanced between treatment groups.*
>
> *In women with PMO (study 216), the overall incidence of malignancies was 4.8% and 4.3% for denosumab and placebo, respectively. No single malignancy differed by > 0.2% in incidence between treatment groups (by MedDRA preferred term); there was no increase in the incidence of malignancy adverse events between treatment groups with prolonged denosumab exposure. Specific to breast cancer events in study 216, the incidence of new breast cancer cases was balanced between the denosumab and placebo groups as was clinical presentation at time of diagnosis (that is, staging and tumour characteristics). In the ongoing safety extension study to 216 (study 289) the incidence of malignancy was similar over time in patients receiving denosumab.*

As stated above, there is no evidence that denosumab adversely affects cancer outcomes in men with prostate cancer as measured by changes in PSA, bone scintography, or overall survival. For the prostate cancer and breast cancer HALT studies, the Delegate cited the hand-tabulated incidence of "metastatic events" by the US FDA discussed at RHDAC. Amgen has not been able to verify the incidence of these events presented by the US FDA. Amgen's analysis shows that in study 138, the subject incidence of adverse events that were determined to be associated with the underlying prostate cancer (by analysing both verbatim terms as well as preferred terms of adverse events in the MedDRA Neoplasms system organ class) was 7.8% (57/731) in the denosumab group compared with 5.0% (36/725 in the placebo group). In both treatment groups, approximately one third of subjects with adverse events indicative of prostate cancer progression had no concomitant PSA rises as defined by an increase from nadir of ≥ 50% and reaching an absolute level of ≥ 2.0 ng/mL. Given the lack of PSA corroboration, these adverse event observations may not represent progression of the underlying cancer, and reveal the limitations of adverse event reporting to accurately reflect progression of prostate cancer. New primary malignancies reported in study 138 were not those typically associated with immunocompromised patients; 5 cases of malignant melanoma occurred in the placebo group and no cases were reported with denosumab. In the 2-year safety follow up for study 138, the incidence of malignancy was not different (and numerically lower for denosumab) between patients receiving placebo and denosumab.

Safety data from PMO and HALT populations is supported by recent results from studies in patients with advanced cancer, some of which has been recently presented.[63,64] *Unblinded Phase III results in 2049 subjects with advanced breast cancer (for example, study 20050136) and 1776 patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma (for example, study 20050244) demonstrate no evidence of increased malignancy risk or of adverse effects on cancer progression or infection, using a denosumab treatment regimen approximately 12 times the proposed PMO or HALT dose relative to an active comparator (zoledronic acid). Cancer progression and overall survival were similar between treatment groups.*

9. ACPM Resolution

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC), 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.

The ACPM recommended approval for the indication:

[63] Stopeck, A; Body, J; Fujiwara et al. Denosumab versus zoledronic acid for the treatment of breast cancer patients with bone metastases: results of a randomized phase 3 study. Joint ECCO 15 – 34th ESMO Multidisciplinary Congress 2009; Berlin. Abstract 2LBA.

[64] Henry D, von Moos R, Vadhan-Raj S et al. A double-blind, randomized study of denosumab versus zoledronic acid for the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. Joint ECCO 15 – 34th ESMO Multidisciplinary Congress 2009; Berlin. Abstract 2LBA.

The treatment of osteoporosis in postmenopausal women. Prolia significantly reduces the risk of vertebral, non-vertebral and hip fractures.

In making this recommendation, the ACPM concluded that the evidence of efficacy for treatment of post menopausal osteoporosis has been satisfactorily demonstrated. The Committee did not consider that explicitly limiting treatment duration to three years is warranted because the BMD results returned to baseline after ceasing denosumab and ongoing studies will have to be promptly submitted for evaluation.

The Committee noted that the safety issues (for example, bone architecture, osteonecrosis of the jaw, immunosuppression, safety in patients who were heavily pretreated - especially with bisphosphonates, delayed healing) have not been completely addressed and therefore considered that the implementation of robust risk management program is an essential pre-requisite for marketing; in particular, adequate post-market surveillance for malignancies and infections is needed. Access to a patient registry is necessary to capture the data of interest. A further potential concern is added toxicity from multiple drug therapy in particular sub-populations for example, rheumatoid arthritis patients.

The Committee agreed with the Delegate that the efficacy data were unconvincing overall for the prostate cancer group. The trial did not target specifically the "at risk" population. The submitted data were based on a heterogeneous group of men with prostate cancer, recruited by a mix of age-related and densitometric criteria. A difficulty with this lies in the heterogeneity of the population studied. Therefore, although the results were statistically significant, the benefit obtained was not considered by the Committee to be clinically meaningful. The specific conditions of registration should include that the new studies and data alluded to in the sponsor's pre-ACPM response be submitted to TGA for evaluation.

10. Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Prolia containing denosumab 60 mg/1mL for

The treatment of osteoporosis in postmenopausal women. Prolia significantly reduces the risk of vertebral, non-vertebral and hip fractures.

TGA refused the registration of Prolia containing denosumab 60 mg/1mL for the indication:

The treatment of bone loss associated with hormone ablation in men with prostate cancer. In men with prostate cancer receiving hormone ablation, PROLIA significantly reduces the risk of vertebral fractures.

Specific conditions of registration include the following:

- Provision of study reports of all ongoing studies on completion, that have been highlighted in the Risk Management Plan as studies that would provide information on identified safety concerns.
- Results of Phase IV studies that are to be conducted in USA and Europe should also be submitted at the same time to Australia as to other agencies.
- Results from patient registries that are to be set up in the USA and Europe should also be submitted to Australia at the same time as to other agencies.

11. Final Outcome

Following the initial decision described above, the sponsor appealed under Section 60 of the Therapeutic Goods Act whereby a review of the initial decision was conducted by the Minister.

The Delegate of the Minister noted the following findings on material facts and the evidence on which his findings were based:

1. On 12 February 2009 Amgen Australia Pty Ltd (the sponsor) submitted a Category 1 submission to the TGA to register three denosumab products for the following proposed indications:
   - "The treatment of osteoporosis in postmenopausal women. Prolia significantly reduces the risk of vertebral, non vertebral and hip fractures.
   - The treatment of bone loss associated with hormone ablation in men with prostate cancer and in women with breast cancer. In men with prostate cancer receiving hormone ablation, Prolia significantly reduces the risk of vertebral fractures."
2. On 17 December 2009 the TGA wrote to the sponsor enclosing a copy of the Delegate's proposed action requesting a pre-ADEC response from the sponsor by 11 January 2010. In this the Delegate outlined that she proposed to reject the indications for denosumab for "the treatment of bone loss associated with hormone ablation in men with prostate cancer and in women with breast cancer due to inadequate evidence of efficacy and safety".
3. On 11 January 2010 the sponsor wrote to the TGA providing a pre-ADEC response to the TGA's request of 17 December 2009. The sponsor stated that it had "elected to defer consideration in Australia of the component of the marketing application for the treatment of bone loss associated with hormone ablation in women with non metastatic breast cancer". The sponsor also stated that "Amgen has added a clarification to the indication in the draft PI that reds "the treatment of bone loss associated with hormone ablation in men with prostate cancer *at increased risk of fracture*."
4. On 4 and 5 February 2010 the Advisory Committee on Prescription Medicines met and resolved that it agreed with the Delegate in not approving the indication for the treatment of bone loss associated with hormone ablation in men with prostate cancer. Its resolution 9388 stated that:
   - "The Committee agrees with the Delegate that the efficacy data were unconvincing overall with the prostate cancer group. The trial did not target specifically the "at risk" population. The submitted data were based on a heterogeneous group of men with prostate cancer, recruited by a mix of age related and densitometric criteria. A difficulty with this lies in the heterogeneity of the population studied. Therefore, although the results were statistically significant, the benefit obtained was not considered by the Committee to be clinically meaningful."
5. On 15 March 2010 the sponsor wrote to the TGA in response to a request dated 23 February 2010 in which the sponsor confirmed that it had withdrawn the indication for "the treatment of bone loss associated with hormone ablation in women with breast cancer".
6. On 17 May 2010 the TGA wrote to the sponsor to see whether it had any further response or information they would like to bring to the Delegate's attention.
7. On 19 May 2010 the sponsor responded to the TGA correspondence dated 17 May 2010 commenting that "Amgen continues to believe a positive risk/benefit profile has been demonstrated for the use of Prolia in the treatment of bone loss associated with hormone ablation in men with prostate cancer.….Amgen duly notifies TGA that it does not intend to withdraw this indication from the Category 1 Application."

8. On 02 June 2010 the TGA wrote to the sponsor to advise that its request to have the product registered for the indication "treatment of bone loss associated with hormone ablation in men with non-metastatic prostate cancer" had been refused. The main reasons for declining this request were "inadequate data submitted on efficacy and safety" and included:

   § "The study submitted to support the indication did not target those who were at risk of having fractures due to bone loss";

   § "Because of this, though the efficacy results showed statistical significance, they were not considered to be clinically meaningful";

   § "The study did not prospectively identify this subpopulation at the recruitment stage";

   § "inadequate safety data…concerns relating to safety were in relation to a higher incidence of cataracts"; and

   § "concerns regarding safety also relate to an increase in metastatic events".

9. On 26 August 2010 the sponsor wrote to the Parliamentary Secretary for Health and Ageing appealing against the Delegate's decision on four issues with the decision-making process, being:

   § Belated concerns about clinical issues with prostate Hormone Ablation Therapy (HALT) indications compromised Amgen's ability to effectively respond;

   § The ground for rejection of "Clinical meaningfulness" is not scientifically based;

   § The *Therapeutic Goods Act 1989* does not provide for a risk-benefit trade-off; and

   § Gender bias considered discriminatory.

10. The EU Guideline on the evaluation of medicinal products in the treatment of primary osteoporosis specifically states that "Bone Mineral Density (BMD) may be the primary end point in exploratory studies but it is not an appropriate surrogate for fracture reduction". It also states that "the primary variable should be assessed as incidence of patients with new fractures, which may be expressed as vertebral fractures or as a composite of hip fractures and the rest of major non vertebral fractures".

11. The EU Guideline "Points to consider on application with 1. Meta-analyses; 2. One Pivotal study dated 31 May 2001" has prerequisites for one pivotal study applications that:

   § The study population should be suitable for extrapolation to the population to be treated;

   § Clinical relevance – the estimated size of treatment benefit must be large enough to be clinically valuable;

   § Similar effects demonstrated in different pre-specified sub-populations. All important end points showing similar findings; and

   § The study has to be particularly compelling with respect to internal and external validity, clinical relevance, statistical significance, data quality, and internal consistency.

12. The study results of study 20040138 in the original Amgen application showed one primary efficacy endpoint only and that is for lumbar spine BMD and this showed a significant increased lumbar spine BMD % relative to placebo to 24 months.

13. The study showed a number of secondary efficacy endpoints with the following results:
    - A significant % increase in femoral neck and total hip BMD to 24 months for the treatment group relative to placebo;
    - A significant % increase in lumbar spine, femoral neck and total hip BMD to 36 months for the treatment group relative to placebo;
    - A non-significant difference in the incidence of any fracture to 36 months for the treatment group relative to placebo;
    - A significant decrease in incidence of new vertebral fractures to 36 months for the treatment group relative to placebo;
    - A non-significant difference in time to first clinical fracture to 36 months for the treatment group relative to placebo; and
    - A non-significant difference in the incidence of any fracture to 24 months for the treatment group relative to placebo.
14. The study showed the following safety related issues:
    - An increase in neoplasms in the treatment group compared to the placebo group of 16.3% vs 11.9%
    - An increase in cataracts in the treatment group compared to the placebo group of 4.7% vs 1.2%, noting that the differences at 1, 2 and 3 years were 2.5% vs 0.4%, 1.9% vs 0.5% and 1.0% vs 0.7% respectively.
    - An increase in primary malignancies in the treatment group vs the placebo group of 5.1% vs 4.6%.
15. The FDA Advisory Committee transcript and FDA presentations at the Advisory Committee reported that there was:
    - an increase in metastatic events in the treatment group compared to the control group of 8.2% vs 5.5%; and
    - that the primary trials evaluating denosumab in the hormone ablation population did not contain "prespecified plans to identify detrimental effects on cancer outcomes such as progression-free-survival (PFS), or overall survival (OS). Overall survival was an exploratory endpoint".

The Delegate of the Minister indicated that his reasons for the decision only deal with the "rejected indication", not the approved indication, as follows.

Efficacy

In the view of the Delegate of the Minister there is insufficient evidence to satisfy him that this product is effective for the treatment of bone loss associated with hormone ablation in men with non-metastatic prostate cancer. The study 2004138 does not provide sufficient evidence for the following reasons.

Although there is no EU guideline relating to secondary osteoporosis, relevant information can be found in the EU Guideline on the evaluation of medicinal products in the treatment of primary osteoporosis which specifically states that "Bone Mineral Density (BMD) may be the primary end point in exploratory studies but it is not an appropriate surrogate for fracture reduction". In study 20040138 fracture reduction is not the primary efficacy endpoint as the

study has BMD as its only primary end point. The study does have fracture reductions as secondary efficacy endpoints and found that there was:

- A significant decrease in incidence of new vertebral fractures to 36 months;
- A non-significant difference in the incidence of any fracture to 36 months;
- A non-significant difference in time to first clinical fracture to 36 months; and
- A non-significant difference in the incidence of any fracture to 24 months.

Therefore the study does not show an overall fracture reduction which should have been the primary efficacy endpoint if it were to support the requested indication. In view of there being a difference in pathophysiology between primary osteoporosis and the potential treatment group for this indication, it would be appropriate to have a significant reduction in overall fractures.

Safety

In the view of the Delegate of the Minister there is also insufficient evidence to satisfy him that this product is safe for the treatment of bone loss associated with hormone ablation in men with non-metastatic prostate cancer. Study 20040138 demonstrates some safety issues which are:

- An increase in neoplasms in the treatment group compared to the control group of 16.3% vs 11.9%;
- An increase in cataracts in the treatment group compared to the control group of 4.7% vs 1.2%, noting that the differences at 1, 2 and 3 years were 2.5% vs 0.4%, 1.9% vs 0.5% and 1.0% vs 0.7% respectively;
- An increase in primary malignancies in the treatment group vs the control group of 5.1% vs 4.6%; and
- an increase in metastatic events in the treatment group compared to the control group of 8.2% vs 5.5%.

Although the issue regrading cataracts is questionable in view of the possible plausibility there is enough concern with all these issues to not satisfy the Delegate of the Minister on the safety of this product. Even the detailed Risk Management Plan will not potentially prevent adverse events occurring in people treated with this product.

The EU Guideline relating to single pivotal studies is also relevant here and the elements mentioned above are:

- The study population should be suitable for extrapolation to the population to be treated – in this case the study population for 20040138 is not the same as that which is now being considered as a treatment population. The study looked at a far wider population of which some did not have bone mineral density loss;
- Clinical relevance – the estimated size of treatment benefit must be large enough to be clinically valuable – the findings of the secondary efficacy endpoints were not consistent and these changes have not been justified as being clinically relevant;
- Similar effects demonstrated in different pre-specified sub-populations. All important end points should show similar findings – the requested indication here is for a sub-population which was not pre-specified in study 20040138 and hence no similar effects have been shown; and

- The study has to be particularly compelling with respect to internal and external validity, clinical relevance, statistical significance, data quality, and internal consistency – which in this case had not occurred.

The above demonstrates significant efficacy and safety issues which are such that they cannot be adequately addressed by the proposed Risk Management Plan which does not even specify malignancy as an Adverse Event of Special Interest (AESI).

The sponsor's appeal also raises four issues for which the Delegate of the Minister has provided comments (italicised text):

- Belated concerns about clinical issues with prostate HALT indications compromised the sponsor's ability to effectively respond. *There does not appear to be any variation from normal TGA processes in dealing with this application. It is normal that a sponsor might not find out about the potential for an adverse outcome to their application until the clinical overview is provided prior to the ACPM meeting. In this case the sponsor was told of the Delegate's view prior to the ACPM meeting and was allowed time to respond;*
- The ground for rejection of "Clinical meaningfulness" is not scientifically based. *Although efficacy might be interpreted as either present or not there is a valid reasoning that efficacy does need to be clinically meaningful. "Clinical meaningfulness" is generally gleaned from studies of other agents used in osteoporosis, and from consensus statements and guideline documents. Although this is not specifically referred to in the Therapeutics Goods Act 1989 it is well accepted that efficacy per se is not relevant. This is especially noted in the EU Guideline which refers to single pivotal studies, mentioned above, where it states that;*
    - *Clinical relevance – the estimated size of treatment benefit must be large enough to be clinically valuable. This alludes to the fact that treatment benefit alone is not sufficient and that it must be "large enough to be clinically valuable".*
- The *Therapeutic Goods Act 1989* does not provide for a risk-benefit trade-off. *When assessing a therapeutic product there is always a risk benefit trade-off considered and this occurs in other regulatory agencies making similar decisions. As an example any anti-cancer drugs will be potentially very risky if given to patients who don't have the cancer and hence would have little benefit, whilst for patients with the cancer targeted there is a potential benefit which might outweigh the risks; and*
- Gender bias considered discriminatory. *This claim is not appropriate as Prolia's approved indication for postmenopausal women involves a completely different target group which does not have prostate cancer and has not had hormone ablation therapy.*

The Delegate of the Minister therefore concurred with the original decision-maker that the applications to register denosumab for the indication "treatment of bone loss associated with hormone ablation in men with non-metastatic prostate cancer" should be rejected. The Delegate of the Minister also concurred with the original decision-maker that the indication of "treatment of osteoporosis in postmenopausal women. Prolia significantly reduces the risk of vertebral, non-vertebral and hip fractures" is approved.

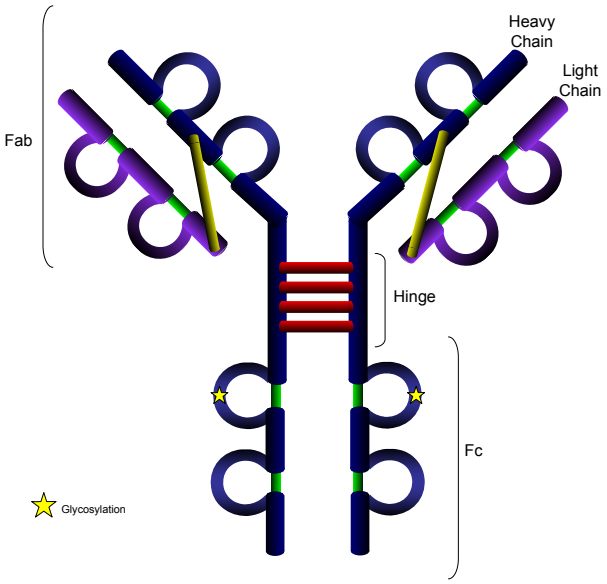
Subject to the Administrative Appeals Tribunal Act 1975, the sponsor has appealed to the Tribunal for review of the Minister's decision. This AusPAR will be amended with the result of this appeal when that result is available.

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

Prolia® 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

Prolia® is a sterile, preservative-free, clear, colourless to slightly yellow solution for injection. The solution may contain trace amounts of translucent to white proteinaceous particles. Each 1 mL single-use pre-filled syringe contains: 60 mg denosumab, 47 mg sorbitol, 1 mg acetate, 0.1 mg polysorbate 20, sodium hydroxide for adjusting to pH 5.2, in Water for Injection, (USP).

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. Osteoclasts play an important role in bone loss associated with postmenopausal osteoporosis and hormone ablation. 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, independent of bone surface. Prevention of RANKL/RANK interaction inhibits osteoclast formation, function and survival, thereby decreasing bone resorption and increasing bone mass and strength in both cortical and trabecular bone.

Pharmacodynamics

In clinical studies, treatment with 60 mg of Prolia® resulted in rapid reduction in the bone resorption marker serum type 1 C-telopeptides (CTX) within 6 hours of SC administration by approximately 70%, with reductions of approximately 85% occurring by 3 days. CTX reductions were maintained over the 6-month dosing interval. At the end of each dosing interval, CTX reductions were partially attenuated from maximal reduction of ≥ 87% to ≥ 45% (range 45% to 80%), reflecting the reversibility of the effects of Prolia® on bone remodelling once serum denosumab levels diminish. These effects were sustained with continued treatment. Consistent with the physiological coupling of bone formation and resorption in skeletal remodeling, subsequent reductions in bone formation markers (e.g. bone specific alkaline phosphatase [BSAP] and serum N-terminal propeptide of type 1 collagen [P1NP]) were observed beginning 1 month after the first dose of Prolia®.

Bone turnover markers (bone resorption and formation markers) generally reached pretreatment levels within 9 months after the last 60 mg subcutaneous dose. Upon re-initiation, the degree of inhibition of CTX by Prolia® was similar to those observed in patients initiating Prolia®.

In a clinical study of postmenopausal women with low bone mass (n = 504) who were previously treated with alendronate for a median of 3 years, those transitioning to receive Prolia® experienced additional reductions in serum CTX, compared with women who remained on alendronate. In this study, the changes in serum calcium were similar between the two groups.

Pharmacokinetics

Following a 60 mg subcutaneous dose of denosumab, bioavailability was 61% and maximum serum denosumab concentrations (C_{max}) of 6 µg/mL (range 1-17 µg/mL) occurred in 10 days (range 2-28 days). After C_{max}, serum levels declined with a half-life of 26 days (range 6-52 days) over a period of 3 months (range 1.5-4.5 months). Fifty-three percent of patients had no measurable amounts of denosumab detected at 6 months post-dose.

No accumulation or change in denosumab pharmacokinetics over time was observed upon subcutaneous multiple-dosing of 60 mg once every 6 months. Denosumab pharmacokinetics was not affected by the formation of binding antibodies to denosumab and was similar in men and women.

Pharmacokinetic analysis was performed to evaluate the effects of demographic characteristics. This analysis showed no notable difference in pharmacokinetics with age (28 to 87 years), race or body weight (36 to140 kg)).

Denosumab is composed solely of amino acids and carbohydrates as native immunoglobulin and is unlikely to be eliminated via hepatic metabolic mechanisms. Based on nonclinical data, 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 was not affected by age (28 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 with varying degrees of renal function, including patients on dialysis, the degree of renal impairment had no effect on the pharmacokinetics of denosumab.

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 5 years tested positive for non neutralising binding antibodies with no evidence of altered pharmacokinetics, toxicity, or clinical response.

CLINICAL TRIALS

Treatment of osteoporosis in postmenopausal women

Independent risk factors, for example, low bone mineral density (BMD), age, the existence of previous fracture, family history of hip fractures, high bone turnover and low body mass index (BMI) should be considered in order to identify women at increased risk of osteoporotic fractures who could benefit from treatment.

FRacture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM):
The efficacy and safety of Prolia® in the treatment of postmenopausal osteoporosis was demonstrated in FREEDOM (Study 20030216), a 3-year, randomised, double-blind, placebo-controlled, multinational study of women with baseline BMD T-scores at the lumbar spine or total hip between -2.5 and -4.0. 7,808 women aged 60 to 91 years were enrolled of whom 23.6% had prevalent vertebral fractures. Women with other diseases or on therapies that may affect bone (e.g. rheumatoid arthritis, osteogenesis imperfecta and Paget's disease) were excluded from this study.

BMD and other individual risk factors were collected for women enrolled in the FREEDOM study. The mean absolute 10-year fracture probability for women enrolled was 18.60% (deciles: 7.9-32.4%) for major osteoporotic fracture and 7.22% (deciles: 1.4-14.9%) for hip fracture, as derived from FRAX®, the WHO Fracture Risk Assessment Tool algorithm.

Women were randomised to receive subcutaneous injections of either Prolia® 60 mg (n = 3,902) or placebo (n = 3,906) once every 6 months. Women received calcium (at least 1,000 mg) and vitamin D (at least 400 IU) supplementation daily. The primary efficacy variable was the incidence of new vertebral fractures. Secondary efficacy variables included the incidence of non-vertebral fractures and hip fractures, assessed at 3 years.

Effect on vertebral fractures
Prolia® significantly reduced the risk of new vertebral fractures at 1, 2 and 3 years ($p < 0.0001$) (see Table 1).

Table 1. The effect of Prolia® on the risk of new vertebral fractures

	Proportion of women with fracture (%)		Absolute risk reduction (%) (95% CI)	Relative risk reduction (%) (95% CI)
	Prolia® n = 3,902 (%)	Placebo n = 3,906 (%)		
0-1 Year	0.9	2.2	1.4 (0.8, 1.9)	61 (42, 74)*
0-2 Years	1.4	5.0	3.5 (2.7, 4.3)	71 (61,79)*
0-3 Years	2.3	7.2	4.8 (3.9, 5.8)	68 (59, 74)*

*p < 0.0001

The reductions in the risk of new vertebral fractures by Prolia® over 3 years were consistent and significant regardless of whether or not women had a prevalent vertebral fracture or history of a non-vertebral fracture, and regardless of baseline age, BMD, bone turnover level and prior use of a medicinal product for osteoporosis.

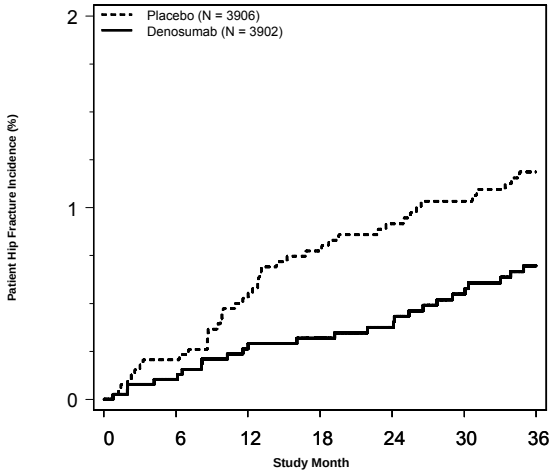
Prolia® also reduced the risk of new vertebral fracture by 65% (6.5% absolute risk reduction, p < 0.0001) in patients at high risk of fractures (defined as women who met ≥ 2 of the 3 following criteria at baseline: age ≥ 70 years, BMD T-score ≤ -3.0 [at lumbar spine, total hip, or femoral neck] or prevalent vertebral fracture).

Prolia® also reduced the risk of new and worsening vertebral fractures (67% relative risk, reduction, 4.8% absolute risk reduction) as well as multiple vertebral fractures (41% relative risk reduction, 1.0% absolute risk reduction) at 3 years, when compared to placebo (all p < 0.0001).

Effect on hip fractures

Prolia® demonstrated a 40% relative reduction (0.5% absolute risk reduction) in the risk of hip fracture over 3 years (p < 0.05) (see Figure 1). The incidence of hip fracture was 0.7% in the Prolia® group compared to 1.2% in the placebo group at 3 years.

Figure 1 Cumulative incidence of hip fractures over 3 years



In women with high fracture risk as defined above by baseline age, BMD and prevalent vertebral fracture, a 48% relative risk reduction was observed with Prolia® (1.1% absolute risk reduction, $p < 0.05$).

Effect on all clinical fractures

Prolia® demonstrated superiority to placebo in reducing the risk of any clinical fractures, clinical (symptomatic) vertebral fractures, non-vertebral fractures (including hip), major non-vertebral fractures and major osteoporotic fractures (see Table 2).

Table 2. The effect of Prolia® on the risk of clinical fractures over 3 years

	Proportion of women with fracture (%)+		Absolute risk reduction (%) (95% CI)	Relative risk reduction (%) (95% CI)
	Prolia® n = 3,902 (%)	Placebo n = 3,906		
Any clinical fracture[1]	7.2	10.2	2.9 (1.6, 4.2)	30 (19, 41)***
Clinical vertebral fracture	0.8	2.6	1.8 (1.2, 2.4)	69 (53, 80)***
Non-vertebral fracture[2]	6.5	8.0	1.5 (0.3, 2.7)	20 (5, 33)**
Major non-vertebral fracture[3]	5.2	6.4	1.2 (0.1, 2.2)	20 (3, 34)*
Major osteoporotic fracture[4]	5.3	8.0	2.7 (1.6, 3.9)	35 (22, 45)***

*p ≤ 0.05; **p = 0.0106, ***p ≤ 0.0001
+ Event rates based on Kaplan-Meier estimates at 3 years
(1) Includes clinical vertebral fractures and non-vertebral fractures
(2) Excludes those of the vertebrae (cervical, thoracic, and lumbar), skull, facial, mandible, metacarpus, and finger and toe phalanges
(3) Includes pelvis, distal femur (i.e. femur excluding hip), proximal tibia (i.e. tibia excluding ankle), ribs, proximal humerus (i.e. humerus excluding elbow), forearm, and hip
(4) Includes clinical vertebral, hip, forearm, and humerus fractures, as defined by the WHO

Women in the FREEDOM study had a mean baseline BMD T-score of -2.2 at the femoral neck. In women with baseline femoral neck BMD ≤ -2.5, Prolia® reduced the incidence of non-vertebral fracture (35% relative risk reduction, 4.1% absolute risk reduction, $p < 0.001$).

The reduction in the incidence of new vertebral fractures, hip fractures and non-vertebral fractures by Prolia® over 3 years were consistent regardless of the 10-year baseline fracture risk as assessed by FRAX.

Effect on bone mineral density

Prolia® significantly increased BMD at all clinical sites measured, relative to treatment with placebo at 1, 2 and 3 years in FREEDOM. Prolia® increased BMD by 9.2% at the lumbar spine, 6.0% at the total hip, 4.8% at the femoral neck, 7.9% at the hip trochanter, 3.5% at the distal 1/3 radius and 4.1% at the total body over 3 years (all $p < 0.0001$). Increases in BMD at lumbar spine, total hip and hip trochanter were observed as early as 1 month after the initial dose. Prolia® increased lumbar spine BMD from baseline in 95% of postmenopausal women at 3 years. Consistent effects on BMD were observed at the lumbar spine regardless of baseline age, race, weight/BMI, BMD and bone turnover level. The effects of Prolia® on bone architecture were evaluated using quantitative computed tomography (QCT) in postmenopausal women with BMD T-score below -2.5 at the lumbar spine or total hip. Treatment with Prolia® increased volumetric trabecular BMD at the lumbar spine, volumetric BMD at the total hip and the volumetric cortical BMD and cortical thickness at the

distal radius.

Study of Transitioning from Alendronate to Denosumab (STAND, Study 20050234) was a double-blind, randomised, alendronate-controlled, study in postmenopausal women with low BMD (T-score between -2.0 and -4.0 at the lumbar spine or total hip) who had received alendronate (70 mg weekly [or equivalent] orally) for at least 6 months preceding study entry. Patients received either Prolia® 60 mg Q6M SC (n = 253) or alendronate orally 70 mg weekly for 12 months (n = 251).

Women who transitioned to receive Prolia® had greater increases in BMD at the total hip (1.9% versus 1.1%, $p < 0.001$; primary efficacy endpoint) after 1 year, compared to those who continued to receive alendronate therapy. Consistently greater increases in BMD were also seen at the lumbar spine, femoral neck, hip trochanter, and distal 1/3 radius in women treated with Prolia®, compared to those who continued to receive alendronate therapy (all $p < 0.05$).

In clinical studies examining the effects of discontinuation of Prolia®, BMD returned to approximately pre-treatment levels and remained above placebo within 18 months of the last dose. These data indicate that continued treatment with Prolia® is required to maintain the effect of the drug. Re-initiation of Prolia® resulted in gains in BMD similar to those when Prolia® was first administered.

Bone Histology
Fifty-three trans-iliac crest bone biopsy specimens were obtained at either 2 years and/or 3 years from 47 postmenopausal women with osteoporosis treated with Prolia®. Fifteen bone biopsy specimens were also obtained after 1 year of treatment with Prolia® from 15 postmenopausal women with low bone mass who had transitioned from previous alendronate therapy. Histology assessments in both studies showed bone of normal architecture and quality, as well as the expected decrease in bone turnover relative to placebo treatment. There was no evidence of mineralisation defects, woven bone or marrow fibrosis.

INDICATIONS

The treatment of osteoporosis in postmenopausal women. Prolia® significantly reduces the risk of vertebral, non-vertebral and hip fractures.

CONTRAINDICATIONS

Hypocalcaemia (See **PRECAUTIONS**).

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

PRECAUTIONS

Hypocalcaemia
Hypocalcaemia must be corrected prior to initiating therapy with Prolia®. In patients predisposed to hypocalcaemia (e.g. history of hypoparathyroidism, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, severe renal impairment [creatinine clearance < 30 mL/min] or receiving dialysis), clinical monitoring of calcium levels is recommended.

Adequate intake of calcium and vitamin D is important in all patients (see **DOSAGE AND ADMINISTRATION** and **ADVERSE EFFECTS**).

Skin Infections

Patients receiving Prolia® may develop skin infections (predominantly cellulitis) leading to hospitalisation (see **ADVERSE EFFECTS**). Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis.

Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been reported in patients treated with denosumab or bisphosphonates, another class of anti-resorptive agents. Most cases have been in cancer patients; however some have occurred in patients with osteoporosis.

ONJ has been reported rarely in clinical studies in patients receiving denosumab at a dose of 60 mg every 6 months for osteoporosis. There have been reports of ONJ in clinical studies in patients with advanced cancer treated with denosumab at the studied dose of 120 mg administered monthly.

Known risk factors for ONJ include a diagnosis of cancer with bone lesions, concomitant therapies (e.g. chemotherapy, antiangiogenic biologics, corticosteroids, radiotherapy to head and neck), poor oral hygiene, dental extractions, and co-morbid disorders (e.g. pre-existing dental disease, anaemia, coagulopathy, infection).

Good oral hygiene practices should be maintained during treatment with Prolia®. If ONJ occurs during treatment with Prolia®, use clinical judgment and guide the management plan of each patient based on individual benefit/risk evaluation.

Paediatric Use

The safety and efficacy of Prolia® in paediatric patients have not been established. Prolia® is not recommended for use in paediatric patients. Adolescent primates dosed with denosumab at 27 and 150 times (10 and 50 mg/kg dose) the clinical exposure based on AUC had abnormal growth plates. In neonatal rats, inhibition of RANKL (target of denosumab therapy) with a construct of osteoprotegerin bound to Fc (OPG-Fc) at high doses was associated with inhibition of bone growth and tooth eruption. Therefore, treatment with denosumab may impair bone growth in children with open growth plates and may inhibit eruption of dentition.

Use in the Elderly

Of the total number of patients in clinical studies of Prolia®, 9,943 patients were ≥ 65 years, while 3,576 were ≥ 75 years. No overall differences in safety or efficacy were observed between these patients and younger patients.

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 150-fold higher than the human exposure at 60 mg subcutaneous administered once every 6 months.

Use in Pregnancy

Pregnancy Category: D

There are no adequate and well-controlled studies of Prolia® in pregnant women. Prolia® is not

recommended for use during pregnancy.

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 100-fold higher than the human exposure. No evidence of harm to the fetus was observed. Preclinical studies in RANK/RANKL-knockout mice suggest absence of RANKL could interfere with the development of lymph nodes in the fetus; the potential for adverse effects on lymph note 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 phenotyic 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). Therefore, treatment with denosumab may impair bone growth in children with open growth plates and may inhibit eruption of dentition. The reversibility of the effects of OPG-Fc has not been examined.

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. A decision on whether to abstain from breast-feeding or to abstain from therapy with Prolia® should be made, taking into account the benefit of breast-feeding to the newborn/infant and the benefit of Prolia® therapy to the woman.

Use in Renal Impairment

No dose adjustment is necessary in patients with renal impairment.

In clinical studies, 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, Hypocalcaemia**).

Use in Hepatic Impairment

The safety and efficacy of Prolia® 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 tumor 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.

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

Treatment of Postmenopausal Osteoporosis

Prolia® has been studied in over 10,500 women with postmenopausal osteoporosis in clinical trials of up to 5 years duration.

The safety of Prolia® in the treatment of postmenopausal osteoporosis was assessed in FREEDOM, a large, 3-year, randomised, double-blind, placebo-controlled, multinational phase III study of 7,808 postmenopausal women aged 60 to 91 years with osteoporosis. A total of 3,886 women were exposed to Prolia® and 3,876 women were exposed to placebo administered once every 6 months as a single 60 mg subcutaneous dose.

The safety of Prolia® was also assessed in a second phase 3 study of similar design. A total of 322 postmenopausal women aged 43 to 83 years with low bone mass were enrolled in this 2-year study. A total of 164 women were exposed to Prolia® and 165 women were exposed to placebo administered once every 6 months as a single 60 mg subcutaneous dose.

In both studies, all women received at least 1000 mg of calcium and 400 IU of vitamin D supplementation per day.

Across the two phase III studies the incidence of all-cause mortality was 1.7% (n = 70) in the Prolia® group and 2.2% (n = 90) in the placebo group. The incidence of serious adverse events was 25.3% in the Prolia® group and 24.3% in the placebo group. The percentage of patients who withdrew from the studies due to adverse events was 2.3% and 2.1% for the Prolia® and placebo groups, respectively.

The most common adverse events reported in studies of women with postmenopausal osteoporosis or low bone mass (n = 8,091), occurring in ≥ 10% of patients either in the Prolia®-treated or placebo group, were back pain (34.1% Prolia®, 34.0% placebo), arthralgia (20.4% in each group), hypertension (15.3% Prolia®, 16.1% placebo), nasopharyngitis (14.8% Prolia®, 15.6% placebo), pain in extremity (11.8% Prolia®, 11.2% placebo) and osteoarthritis (10.9% Prolia®, 11.1% placebo).

Adverse reactions defined as adverse events reported in at least 2% of postmenopausal women with osteoporosis or low bone mass (n = 8,091) and at least 1% more frequently in the Prolia®-treated women than in the placebo-treated women were: hypercholesterolemia (7.0% Prolia®, 5.9% placebo) and eczema (includes dermatitis, allergic dermatitis, atopic dermatitis and contact dermatitis) (3.1% Prolia®, 1.7% placebo).

In STAND, a double-blind, randomised, alendronate-controlled, study in postmenopausal women with low bone mass who had received alendronate for at least 6 months preceding study entry, patients received either Prolia® 60 mg Q6M SC (n = 253) or alendronate orally 70 mg weekly for 12 months (n = 249). The safety profile was similar for patients transitioning from alendronate to denosumab and those continuing on alendronate therapy, including the overall incidence of adverse events and serious adverse events. Eight patients (3.2%) in the Prolia® group and 4 patients (1.6%) in the alendronate group reported adverse events of fracture.

Hypocalcaemia
In two phase III placebo-controlled clinical trials in postmenopausal women with osteoporosis, approximately 0.05% (2 of 4,050) of patients had declines of serum calcium levels (less than 1.88 mmol/l) following Prolia® administration.

Skin Infections
In two phase III placebo-controlled clinical trials in postmenopausal women with osteoporosis, skin infections leading to hospitalisation were reported more frequently in the Prolia® (0.4%, 16 of 4,050) versus the placebo (0.1%, 3 of 4,041) groups, respectively. These cases were predominantly cellulitis. The overall incidence of skin infections was similar between the Prolia® (1.5%, 59 of 4,050) and placebo groups (1.2%, 50 of 4,041).

Pancreatitis
Pancreatitis was reported in 4 patients (0.1%) in the placebo and 8 patients (0.2%) in the Prolia® groups. Several patients had a prior history of pancreatitis or a confounding event (e.g. gallstones). The time from product administration to event occurrence was variable.

Osteonecrosis of the Jaw (ONJ)
In the osteoporosis clinical trial program, ONJ was reported rarely in patients treated with Prolia®.

DOSAGE AND ADMINISTRATION

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

The recommended dose of Prolia® is a single subcutaneous (SC) injection of 60 mg, once every 6 months.

To reduce the risk of hypocalcaemia, patients must be adequately supplemented with calcium and vitamin D (see **PRECAUTIONS, Hypocalcaemia**). In the major clinical trials of Prolia®, daily supplementation with 1000 mg of calcium and at least 400 IU vitamin D was recommended.

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

Prolia® is a sterile and preservative-free product. Before administration, the Prolia® solution should be inspected for particulate matter and discolouration. Do not use if the solution is cloudy or discoloured. Do not excessively shake the pre-filled syringe. To avoid discomfort at the site of injection, allow the pre-filled syringe to reach room temperature (up to 25°C) before injecting, and inject slowly. Inject the entire contents of the pre-filled syringe.

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

OVERDOSAGE

There is no experience with overdosage with Prolia®. Prolia® 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 no additional adverse effects were observed.

PRESENTATION AND STORAGE CONDITIONS

Prolia® 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 1 mL single-use pre-filled syringe contains 60 mg of denosumab in 1 mL (60 mg/mL). Product is for single-use in one patient only. Dispose of any medicinal product remaining in the pre-filled syringe.

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

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

Pre-filled syringe with automatic needle guard:
Pack size of one, presented in blistered packaging.

The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4 Prescription Medicine

DATE OF APPROVAL

2 June 2010

Therapeutic Goods Administration

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