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BACKGROUND INFORMATION

FOR THE MEETING OF THE

ADVISORY COMMITTEE FOR REPRODUCTIVE HEALTH DRUGS

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List of Abbreviations

Abbreviation or Term	Definition/Explanation
ACO	Amgen Colorado
ADT	Androgen deprivation therapy
AE	Adverse event
AIT	Aromatase inhibitor therapy
AMG 162	Denosumab
ANCOVA	Analysis of covariance
ATAC	Arimidex, Tamoxifen, Alone or in Combination (trial)
ATO	Amgen Thousand Oaks
BA	Bioavailability
BE	Bioequivalence
BLA	Biologics License Application
BMD	Bone mineral density
BMI	Body mass index
BSAP	Bone-specific alkaline phosphate
BTM	Bone turnover marker
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMS	Centers for Medicare & Medicaid Services
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CTIBL	Cancer-treatment-induced bone loss
CTX1	Serum type 1 C-telopeptide
Denosumab	Fully human monoclonal antibody to RANKL; international nonproprietary name for AMG 162
DMC	Data monitoring committee
DPMGSA	Denosumab Post-Marketing Global Safety Assessment
DXA	Dual energy x-ray absorptiometry
ECG	Electrocardiogram
ER	Estrogen receptor
ESRD	End stage renal disease
FDA	Food and Drug Administration
HALT	Hormone ablation therapy
huRANKL	Human RANKL
IAS	Integrated Analysis of Safety
IgG	Immunoglobulin G
IL-1	interleukin 1
IV	Intravenous(ly)

List of Abbreviations

Abbreviation or Term	Definition/Explanation
KPMCP	Kaiser Permanente Medical Care Program
LHRH	Luteinizing hormone releasing hormone
LOCF	Last observation carried forward
LOCS III	Lens Opacities Classification System III
MedDRA	Medical Dictionary for Regulatory Activities
MORE	Multiple Outcomes of Raloxifene (study)
microCT	Micro-computerized tomography
NIH	National Institutes of Health
ONJ	Osteonecrosis of the jaw
OPG	Osteoprotegerin
P1NP	Intact N-terminal propeptide of type 1 procollagen
PD	Pharmacodynamics
PK	Pharmacokinetics
PMO	Postmenopausal osteoporosis
PSA	Prostate-specific antigen
PTH	Parathyroid hormone
Q3M	Every 3 months
Q6M	Every 6 months
QM	Monthly
QW	Weekly
RUTH	Raloxifene Use for the Heart (study)
SAE	Serious adverse event
SC	Subcutaneous(ly)
SCS	Summary of Clinical Safety
SD	Standard deviation
SIR	Standardized incidence ratios
SEER	Surveillance, Epidemiology and End Results (program)
SNHRD	Scandinavian National Health Registry Databases
SRE	Skeletal-related event
TNF	Tumor necrosis factor
TRAP 5b	Tartrate-resistant acid phosphatase 5b
WHO	World Health Organization

1. Executive Summary

Introduction

- Biologics License Application (BLA) 125320 was submitted by Amgen Inc. to FDA on 19 December 2008 to request consideration of approval for denosumab, a fully human monoclonal antibody that inhibits RANK ligand (RANKL), thus inhibiting osteoclast-mediated bone resorption, with proposed indications for:
 - treatment of osteoporosis in postmenopausal women,
 - prevention of osteoporosis in postmenopausal women,
 - treatment and prevention of bone loss associated with hormone ablation therapy with breast cancer, and
 - treatment and prevention of bone loss associated with hormone ablation therapy in patients with prostate cancer.
- Denosumab was evaluated in indications for both postmenopausal osteoporosis (PMO) and bone loss due to hormone ablation therapy (HALT) based on the common underlying mechanism for osteoclast-mediated bone loss and the similar pharmacokinetics and pharmacodynamic effects with the 60 mg every 6 months (Q6M) dose in these populations.
- The submitted application summarized data from 30 clinical studies which included approximately 10,500 subjects with PMO and approximately 1700 subjects with nonmetastatic cancer treated with HALT.

Burden of Disease and Limitations of Current Therapies for PMO and Bone Loss Due to HALT

- PMO is a major public health concern, resulting in significant clinical morbidity, mortality, and healthcare burden. Similarly, bone loss due to HALT in patients with breast cancer and prostate cancer is associated with significant morbidity in addition to the underlying cancer.
- PMO and bone loss due to HALT are largely due to increased osteoclast-mediated bone resorption following reductions in sex-hormone levels which result in accelerated bone loss and increased fracture risk.
- PMO is undertreated, and limitations of current therapies (including tolerability and adherence) can reduce their effectiveness for fracture risk reduction in practice.
- The consequences of bone loss due to HALT are underappreciated, and no therapies are currently approved for treatment of this condition.

Denosumab Background

- Denosumab is a fully human IgG2 monoclonal antibody that binds to RANKL and prevents activation of RANK, thereby inhibiting osteoclast formation, function, and survival and decreasing the number of osteoclasts.
- Denosumab thereby decreases bone resorption and increases cortical and trabecular bone mass and bone strength.

Dose Regimen in PMO and Bone Loss Associated With HALT

- The 60 mg Q6M dose regimen was the lowest dose at the least frequent interval that resulted in maximal bone mineral density (BMD) gains across skeletal sites.
- Patient preference for a Q6M subcutaneous (SC) injection over a QW oral (PO) tablet, which was demonstrated in 2 head-to-head studies comparing denosumab to alendronate, may contribute to patient adherence and clinical outcomes.

Clinical Efficacy of Denosumab for the Treatment and Prevention of PMO

- The clinical development program in PMO is supported by the following key studies:
 - Pivotal, phase 3, treatment of PMO fracture study (20030216) (n = 7808)
 - Pivotal, phase 3, prevention of PMO study (20040132) (n = 332)
 - Phase 3, head-to-head vs alendronate (naive) study (20050141) (n = 1189)
 - Phase 3, head-to-head vs alendronate (transition) study (20050234) (n = 504)
 - Phase 2, dose-ranging study (20010223) (n = 412)
- Denosumab statistically significantly reduced the risk (compared with placebo) of new vertebral fractures by 68%, nonvertebral fractures by 20%, and hip fractures by 40%. Significant vertebral fracture reduction was observed at 1 year and was sustained for 3 years. Open-label data will be collected for up to 10 years of total exposure to denosumab.
- Consistent with denosumab's mechanism of action, bone turnover markers and histomorphometric parameters showed findings consistent with decreased bone remodeling.
- Denosumab significantly increased BMD at all skeletal sites measured.
- In 2 active-controlled studies, BMD increases were significantly greater than those observed with alendronate.
- Increases in BMD and decreases in bone turnover markers due to denosumab treatment were reversible upon discontinuation of denosumab therapy.
- Bone histology in denosumab-treated subjects showed that bone was of normal quality.

Clinical Efficacy of Denosumab for the Treatment of Bone Loss Due to HALT

- The clinical development program in bone loss due to HALT is supported by the following key studies:
 - Pivotal, phase 3, HALT prostate cancer study (20040138) (n = 1468)
 - Pivotal, phase 3, HALT breast cancer study (20040135) (n = 252)
- Denosumab significantly increased BMD at all skeletal sites in both women and men with bone loss due to HALT. Increases were consistent with those observed in women with PMO.
- Denosumab reduced the risk of new vertebral fracture by 62% in men with prostate cancer receiving androgen deprivation therapy (ADT). Effects were

observed at 1 year and were sustained for 3 years. Reductions in vertebral fracture risk were consistent with those observed in women with PMO.

Clinical Safety of Denosumab

- The PMO and HALT Combined Safety Analysis Set encompassed approximately 13,000 patient-years of exposure to denosumab (approximately 11,000 patient years for PMO and 2,000 patient-years for HALT) with similar exposure to placebo. Subjects were exposed to denosumab for up to 5 years. Open-label data will be collected from the ongoing clinical trials for up to 10 years of total exposure to denosumab for further evaluation of safety.
- Denosumab administered SC was generally well tolerated with injection-site reaction incidence similar to placebo (< 1%).
- Denosumab caused transient and mild decreases in serum calcium that were generally within the normal range and asymptomatic. All subjects in the phase 3 and ongoing studies received or will receive calcium and vitamin D supplementation.
- In women with PMO, more subjects in the denosumab group experienced skin infections requiring hospitalization (0.4% denosumab, 0.1% placebo); events were primarily cellulitis. Overall, there were no differences in the incidences of adverse events of infections, including opportunistic infections, between denosumab- and placebo-treated subjects in the PMO and HALT pivotal studies. The incidences of most infections reported as serious adverse events (SAEs) were balanced indicating no generalized increase in the risk of SAEs of infection.
- In men with prostate cancer receiving ADT, more subjects in the denosumab group experienced adverse events of cataracts (4.7% denosumab, 1.2% placebo). There were no differences in the incidences of adverse events of cataracts between denosumab- and placebo-treated subjects in the PMO pivotal studies (5.8%, 6.3%) and in women with breast cancer receiving aromatase inhibitor therapy (AIT) (0.8%, 0.8%).
- In the PMO and HALT programs, no adverse events were confirmed by an external, independent adjudication as osteonecrosis of the jaw (ONJ).
- The incidences of cardiovascular events, fracture healing complications, malignancies, and drug hypersensitivity reactions were specifically identified as adverse events of interest and were similar in the denosumab and placebo groups.
- No antibodies that neutralize denosumab have been observed.
- The number of deaths was balanced in the denosumab and placebo groups.

Pharmacovigilance Program

- The size of the denosumab clinical program provided 80% power to detect a 2-fold increase in background events occurring at a rate of 4/1000 or higher.
- A systematic and comprehensive postmarketing pharmacovigilance program for denosumab is proposed. Risk assessment will include evaluation of ongoing long-term safety studies in PMO and HALT and from the advanced cancer program. More than 8000 patients are currently enrolled with denosumab exposure planned for up to 10 years.

- A randomized, placebo-controlled clinical trial will evaluate the risk of cataracts in men with prostate cancer receiving ADT.
- A postmarketing pharmacoepidemiology observational study using available health systems databases is planned to include approximately 380,000 women with PMO exposed to denosumab for up to 5 years in real world settings. The study is designed to have 80% power to detect a 2-fold increase in risk in the exposed cohort, compared with an unexposed cohort, for events with an incidence rate in the unexposed cohort as low as 2.5/100,000.
- Risks for hypocalcemia and skin infections leading to hospitalization, and potential risk for ONJ, can be appropriately managed through product labeling and continued risk assessment through the pharmacovigilance program.

Conclusion

- As demonstrated by data from an extensive development program, denosumab, administered SC at a dose of 60 mg Q6M, has a favorable benefit-risk profile in the indications sought:
 - treatment of osteoporosis in postmenopausal women,
 - prevention of osteoporosis in postmenopausal women,
 - treatment and prevention of bone loss associated with hormone ablation therapy with breast cancer, and
 - treatment and prevention of bone loss associated with hormone ablation therapy in patients with prostate cancer.

2. Burden of Disease and Limitations of Current Therapies for PMO and Bone Loss Due to HALT

2.1 Key Points

- PMO is a major public health concern, resulting in significant clinical morbidity, mortality, and healthcare burden. Similarly, bone loss due to HALT in patients with breast cancer and prostate cancer is associated with significant morbidity in addition to the underlying cancer.
- PMO and bone loss due to HALT are largely due to increased osteoclast-mediated bone resorption following reductions in sex-hormone levels which result in accelerated bone loss and increased fracture risk.
- PMO is undertreated, and limitations of current therapies (including tolerability and adherence) can reduce their effectiveness for fracture risk reduction in practice.
- The consequences of bone loss due to HALT are underappreciated, and no therapies are currently approved for treatment of this condition.

2.2 PMO

2.2.1 Disease Background for PMO

Osteoporosis is a common, systemic skeletal disorder characterized by low bone mass and compromised bone strength predisposing individuals to an increased risk of fracture ([NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, 2001](#)). Osteoporosis has been operationally defined by the World Health Organization (WHO) as bone mineral density (BMD) at the lumbar spine that is more than 2.5 standard deviations below the average value for young healthy women (ie, a T-score ≤ -2.5) ([Kanis, 1994](#)). The risk of fracture increases with decreasing bone BMD and increasing age ([Cummings et al, 2006](#); [Johnell et al, 2005](#); [Kanis et al, 2001](#)). Other risk factors for fractures include a history of previous fractures, a parental history of hip fracture, current tobacco smoking, long-term use of oral glucocorticoids, and high alcohol consumption ([Kanis et al, 2001](#)). Algorithms to predict fracture risk have been developed recently, based on BMD and other risk factors ([Kanis et al, 2008](#)).

Osteoporosis is a major public health threat; the prevalence of osteoporosis has been estimated to be as high as 200 million people worldwide ([Reginster and Burlet, 2006](#)). About 10 million Americans are thought to have osteoporosis ([National Osteoporosis Foundation, 2008](#)); in addition, 34 million men and women have low bone mass and are at increased risk for osteoporosis and its potential complications ([Looker et al, 1997](#)).

The morbidity and mortality associated with osteoporosis-related fractures have significant clinical, human, and economic costs (Kanis et al, 2004a; Cree et al, 2003). About half of women are at lifetime risk of having an osteoporotic fracture (Dennison et al, 2006). In the US, an estimated 2 million fractures related to osteoporosis occurred in 2005 with a projected 3.5 million osteoporotic fractures in 2025 (Burge et al, 2007).

Vertebral crush fracture is the hallmark of osteoporosis and is a marker of disease progression and severity. More than two thirds of new vertebral fractures are not diagnosed clinically and are only identified radiographically (vertebral deformities) (Kanis et al, 2004b; Nevitt et al, 1998). The remaining third of the vertebral fractures are clinically apparent and cause increases in back pain and functional limitations (Nevitt et al, 1998). Prevalent vertebral fractures, including asymptomatic vertebral fractures, predict subsequent vertebral fractures and are associated with long-term back pain, disabilities, and morbidity (Papaioannou et al, 2002; Tosteson et al, 2001; Nevitt et al, 2000). In addition, prevalent vertebral fractures are strong independent predictors of other osteoporosis fractures, including those of the hip (Kanis et al, 2005; Kanis et al, 2004b).

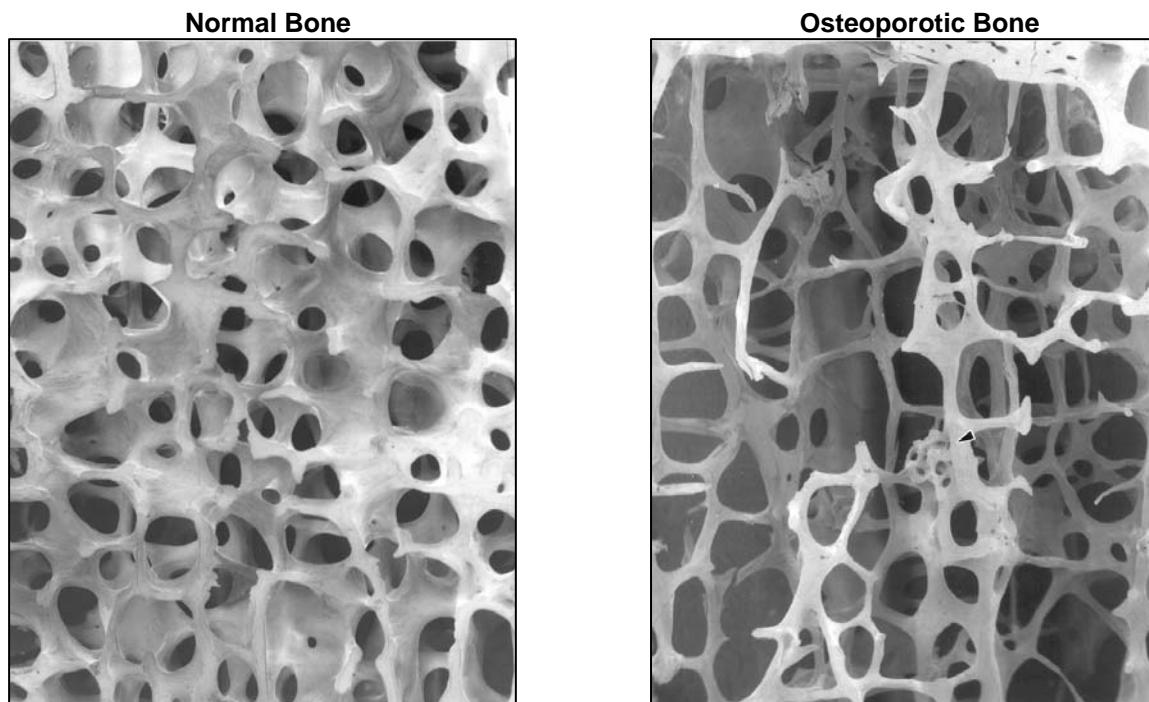
Hip fractures are the most serious of osteoporotic fractures and have immediate clinical consequences as they almost always require surgical repair and often result in disability and loss of independence (Cummings and Melton, 2002; Cree et al, 2000). Mortality rates in the first year after a hip or vertebral fracture are significantly higher than in the general population, and approximately 20% of women die within a year of hip fracture (Johnell et al, 2004; Leibson et al, 2002; Cooper et al, 1993). An increased risk of death may persist for at least 5 years afterwards (Magaziner et al, 1997). Since it is likely that at least some of the increase in mortality rate is either a direct or indirect consequence of the fractures, it is plausible that a therapy that prevents hip fracture will increase survival.

2.2.2 Pathophysiology of PMO

Bone remodeling is the result of continuous turnover of bone matrix and mineral. The process, which is controlled by a complex signaling network, is characterized by resorption of bone by osteoclasts and formation of new bone by osteoblasts. Aging and menopause-associated decreases in estrogen levels increase bone remodeling rate and result in a relative imbalance between bone resorption and formation. Excessive bone resorption results from increased osteoclast formation, function, and survival. This process is driven by regulatory cytokines, of which RANK ligand (RANKL) is essential. Excessive bone resorption reduces bone mass and causes microarchitectural

deterioration (ie, perforation and loss of cancellous bone, cortical thinning, and increased cortical porosity) with reduced bone strength and increased susceptibility to fracture (Figure 1). These processes can lead to osteoporosis.

Figure 1. Example of Microarchitecture Deterioration in Untreated Osteoporosis (Photomicrographs of Bone Biopsies)



Images courtesy of David W Dempster, PhD. Reproduced with permission.

2.2.3 Current Treatments for PMO and Unmet Need

The aim of osteoporosis interventions is to either minimize risk factors for fracture or to improve bone strength through pharmacologic therapy. Initial therapy generally entails nonpharmacologic recommendations, including calcium and vitamin D supplementation (which have mild antiresorptive effects), weight-bearing and muscle-strengthening exercise, and avoiding tobacco smoking and excessive alcohol intake ([Dawson-Hughes and National Osteoporosis Foundation Guide Committee, 2008](#)).

Based on the pathophysiology of bone loss, the aim of pharmacological intervention in the treatment of osteoporosis is to decrease the risk for fracture by slowing the deterioration of bone mass and microarchitecture. This can be accomplished either by reducing bone resorption (antiresorptives) or increasing bone formation (anabolics).

Several effective therapies for osteoporosis are available in the US. Antiresorptive therapies decrease bone resorption by inhibiting osteoclasts while anabolic agents

increase bone formation by stimulating osteoblasts. Antiresorptive therapies include estrogens, estrogen receptor agonists/antagonists, and bisphosphonates ([Appendix 1](#)). Teriparatide (parathyroid hormone [PTH] 1-34) is the only anabolic therapy approved in the US. Antiresorptives are used much more frequently than anabolic therapies. Bisphosphonates are the most commonly used antiresorptive agents, among which alendronate is the most often prescribed.

Estrogen receptor agonists/antagonists mimic the effects of estrogen at the estrogen receptor in some tissues (eg, bone) and antagonize the effects of estrogen at its receptor in other tissues (eg, breast). As a result, osteoclast activity is inhibited and bone loss is reduced. Raloxifene is the only estrogen receptor agonist/antagonist currently approved to treat PMO in the US. It has been shown to reduce the risk of vertebral fractures by 30% to 55%; no effect on nonvertebral and hip fractures has been demonstrated ([Ettinger et al, 1999](#); [Evista Prescribing Information, 2008](#)). Raloxifene has also been shown to decrease breast cancer risk by 66% in patients with estrogen receptor (ER) positive tumors ([Martino et al, 2004](#)).

The bisphosphonates are synthetic analogs of pyrophosphate that bind to the hydroxyapatite in bone. The term “bisphosphonates” includes older agents and the second-generation agents, often referred to as “aminobisphosphonates” (alendronate, ibandronate, risedronate, and zoledronic acid). The broader term is used in this document.

Among the bisphosphonates, alendronate and risedronate are administered orally (PO), zoledronic acid is administered intravenously (IV), and ibandronate is administered either PO or IV. Bisphosphonates are more frequently administered PO than IV. Efficacy appears to vary somewhat between approved oral agents ([Appendix 1](#)) but no head-to-head fracture studies have been conducted to establish their relative effectiveness.

Although bisphosphonates have provided valuable therapeutic options to patients and health-care providers, a number of factors have limited their effectiveness outside of the clinical trial setting, including perceived side effects and low adherence. Long-term adherence to the oral dosing regimens is poor. Adherence estimates for oral bisphosphonates after 1 year range from 24% to 61% ([Rabenda et al, 2008](#); [van den Boogaard et al, 2006](#); [McCombs et al, 2004](#); [Weycker et al, 2006](#)). (For simplicity, the term “adherence” is used throughout this document to refer interchangeably to the concepts of compliance and persistence with therapy.) Low adherence with oral

bisphosphonates has been shown, in a large claims database, to be associated with attenuation of the efficacy of these agents ([Siris et al, 2006](#)).

Teriparatide, a PTH analog, increases osteoblastic activity to a greater extent than osteoclastic activity, providing a net gain in new bone. Teriparatide, injected subcutaneously (SC) daily, showed robust effects on new vertebral fractures (65% relative risk reduction) and nonvertebral fractures (53% relative risk reduction), but hip fracture reduction was not demonstrated ([Neer et al, 2001](#)). Teriparatide cannot be given beyond 24 months due to the finding of osteosarcoma in rats.

Although several approved therapies are available for the treatment of osteoporosis, there remains considerable unmet need. Large claims databases suggest that approximately 54% of women diagnosed with osteoporosis are not being treated (Amgen data on file). In addition, treatment of osteoporosis is prescribed for only a minority of older patients who experience fractures (26%, [Simonelli et al, 2003](#); 22%, [Solomon et al, 2003](#); 5%, [Kamel et al, 2000](#)). Thus, osteoporosis is undertreated and therapeutic alternatives are needed.

2.3 Bone Loss Due to HALT

Cancer treatments may induce bone loss, ie, cancer-treatment–induced bone loss (CTIBL). The most common form of CTIBL is bone loss due to hormone ablation therapy (HALT). HALT comprises aromatase inhibitor therapy (AIT) for breast cancer and androgen deprivation therapy (ADT) for prostate cancer.

The most commonly used aromatase inhibitors are the third-generation molecules letrozole, anastrozole, and exemestane; these block the production of estrogens from androgens in the process called “aromatization.”

The most common methods of androgen deprivation in men are luteinizing hormone releasing hormone (LHRH) agonists or antagonists (eg, leuprolide and goserelin) and surgical castration (bilateral orchiectomy).

2.3.1 Disease Background for Bone Loss Due to HALT

In Western industrialized countries, breast and prostate cancer constitute the most common malignancies in women and men, respectively. According to estimates from the American Cancer Society, over 192,000 women in the United States will be found to have invasive breast cancer in 2009, with over 40,000 expected deaths ([American Cancer Society, 2009a](#)); for prostate cancer, over 192,000 new cases are expected in 2009, with over 27,000 expected deaths ([American Cancer Society, 2009b](#)).

Because hormone ablation has been found to confer prolonged tumor-specific survival by inhibiting growth of most prostate cancers and ER-positive breast cancer, such regimens are frequently used as first-line, second-line, and adjuvant antineoplastic therapy ([Wu and Goss, 2007](#); [Goss et al, 2003](#); [Bolla et al, 2002](#); [Messing et al, 1999](#)).

In postmenopausal women with breast cancer, the concentration of estradiol in breast-carcinoma tissue is about 10 times the concentration in plasma, probably in part because of the presence of intratumoral aromatase ([Thijssen and Blankenstein, 1989](#)). Potent blockade of estrogen production using aromatase inhibitors lowers the estrogen level in the tumor and reduces circulating estrogen to 1% to 10% of pretreatment levels in patients with ER+ or ER-/PR+ ([Lake and Hudis, 2002](#)). Aromatase inhibitors have been shown to be superior to the available hormonal therapy in multiple efficacy endpoints, including objective response rate (ORR), time to progression (TTP), and possibly survival, in both first and second line settings in postmenopausal women with advanced hormone receptor positive breast tumors ([Dombernowsky et al, 1998](#); [Nabholtz et al, 2000](#); [Mouridsen et al, 2003](#)). The benefit of aromatase inhibitors has been also shown in the adjuvant setting in postmenopausal women with hormone receptor positive tumors, either as the first-line therapy or after completing 5 years of initial adjuvant therapy with tamoxifen ([Goss et al, 2003](#)).

In men with prostate cancer, ADT with a gonadotropin-releasing hormone (GnRH) agonist is the mainstay of treatment for patients with metastatic disease. ADT lowers testosterone levels either by surgical castration or by using therapeutics that suppress pituitary gonadotropins (luteinizing hormone and follicle stimulating hormone). Since testosterone is the substrate for aromatase conversion to estrogen, the reduction in testosterone levels subsequently also reduces circulating estrogen levels. The benefit of early initiation of ADT has been shown in men with locally advanced, nonmetastatic prostate cancer ([Medical Research Council Prostate Cancer Working Party Investigators Group, 1997](#)); with locally advanced prostate cancer treated with radiation therapy ([Bolla et al, 1997](#)); and with node-positive prostate cancer treated with radiation therapy and pelvic lymphadenectomy ([Messing et al, 1999](#)). In addition, GnRH agonists are increasingly used when men experience a rising prostate specific antigen (PSA) as the only evidence of disease recurrence after a local therapy.

Reductions in estrogen and testosterone due to the hormone ablation therapies described above lead to increases in bone turnover, resulting in bone loss and increased fracture risk. AIT for postmenopausal women with ER-positive breast cancer

compounds the bone loss associated with age-related postmenopausal status ([Hirbe et al, 2006](#)). AIT has been shown to be accompanied by morbidity, as manifested by increased bone loss (up to 3% per year at the lumbar spine and 2% per year at the total hip) and increased risk for fracture (11% to 49% increase) ([Reid et al, 2008](#); [Coates et al, 2007](#); [The ATAC Trialists' Group, 2005](#); [Baum et al, 2003](#)). The medical burden of fractures attributable to AIT also results in significant cost ([Zhou et al, 2003](#)). This fracture burden is likely to grow due to the expected future increase both in number of patients treated as well as duration of therapy ([Wu and Goss, 2007](#)).

Similarly, bone loss is accelerated in men with prostate cancer who are undergoing ADT, either by surgical castration (bilateral orchiectomy) or chemical castration (luteinizing hormone releasing hormone [LHRH] agonists or antagonists) ([Daniell, 1997](#)). ADT has also been shown to be accompanied by morbidity, as manifested by increased bone loss (up to 5% per year at the lumbar spine and 3% per year at the total hip) and increased risk for fracture (13% to 53% increase) ([Shahinian et al, 2005](#); [Smith et al, 2005](#); [Melton et al, 2003](#); [Daniell, 1997](#)). According to [Shahinian et al \(2005\)](#), men with prostate cancer who are undergoing ADT are at significantly higher risk than age-matched controls of developing osteoporotic fractures of the spine, hip, pelvis, extremities, ribs, and other nonvertebral sites. [Oefelein et al \(2002\)](#) reported that fractures at any location were associated with shorter overall survival in men receiving ADT for prostate cancer. The clinical impact of fractures is further highlighted by a 1-year mortality rate of 31% after hip fracture in older men, a mortality rate almost twice that of older women with hip fracture ([Campion and Maricic, 2003](#)). In addition to the medical and quality-of-life burdens, the economic impact of ADT-related fractures is of increasing concern ([Krupski et al, 2007](#)). The excess or increased mortality following fracture has been mostly investigated as all-cause mortality in the period after various types of fractures, and may be due, at least in part, to underlying comorbidities, including immobility, rather than the fracture event itself.

2.3.2 Pathophysiology of Bone Loss Due to HALT

Estrogen (including all active endogenous forms) is a major determinant of skeletal integrity in both women (as described above for PMO, [Section 2.2.2](#)) and men ([Khosla et al, 1998](#)). Testosterone also is important for skeletal integrity in men ([Stoch et al, 2001](#); [Falahati-Nini et al, 2000](#)), and a significant portion of testosterone's effect on preserving skeletal integrity in men is exerted by aromatization to estrogen ([Leder et al, 2003](#)). Hormone ablation therapies reduce the already low levels of bioavailable serum

estrogen in both women and men treated with antineoplastic regimens ([Khosla et al, 1998](#)). In men, androgen deprivation by LHRH agonists has been shown to decrease serum concentrations of testosterone by > 90% and estrogen by approximately 75% ([Smith et al, 2001](#); [Stoch et al, 2001](#)). The consequent bone loss and increased fracture risk ([ATAC Trialists' Group, 2005](#); [Shahinian et al, 2005](#)) are increasingly recognized as an unmet medical need ([Smith, 2008](#); [Body et al, 2007](#); [Guise, 2006](#)).

2.3.3 Current Treatments for Bone Loss Due to HALT and Unmet Need

No therapies are currently approved to treat bone loss due to HALT. Guidelines and expert opinion-based medical recommendations for the management of bone health for patients undergoing HALT include lifestyle modifications (eg, smoking cessation, regular exercise) and supplemental dietary calcium and vitamin D as well as treatment with bisphosphonates ([NCCN, 2008](#); [Body et al, 2007](#); [Hillner et al, 2003](#)). There is limited evidence for a beneficial effect of bisphosphonates on bone loss and no evidence for a beneficial effect of bisphosphonates on fracture risk in these settings ([Brufsky et al, 2008](#); [Bundred et al, 2008](#); [Saad et al, 2008](#); [Smith, 2008](#); [Brufsky et al, 2007](#)).

3. Denosumab Background

3.1 Key Points

- Denosumab is a fully human IgG2 monoclonal antibody that binds to RANKL and prevents activation of RANK, thereby inhibiting osteoclast formation, function, and survival and decreasing the number of osteoclasts.
- Denosumab thereby decreases bone resorption and increases cortical and trabecular bone mass and bone strength.

3.2 Biology of RANKL

Based on similarities in structure, RANK ligand (RANKL) has been classified as a member of the tumor necrosis factor (TNF) family of proteins. Functionally, RANKL has been well documented as an essential factor in osteoclast formation, function, and survival ([Burgess et al, 1999](#); [Lacey et al, 1998](#); [Yasuda et al, 1998](#)); the osteoclast is the sole somatic cell type responsible for bone resorption. The effects of RANKL are exclusively mediated by its activation of a single receptor called RANK, which is found on mature osteoclasts and on their precursors ([Hsu et al, 1999](#)). RANKL is a dominant regulator of bone resorption that permits or mediates the pro-resorptive effects of numerous hormones and cytokines including PTH, interleukin 1(IL-1), and vitamin D3 ([Kearns et al, 2008](#)). RANKL production is suppressed by estrogens ([Eghbali-Fatourechi et al, 2003](#)), and a reduction in estrogens with menopause or by surgical hormone ablation (ovariectomy) is associated with increased RANKL, increased bone resorption, and significant bone loss ([Eghbali-Fatourechi et al, 2003](#); [Ominsky et al, 2008](#)). Inactivation of RANK or RANKL in knockout mice resulted in markedly reduced osteoclast numbers and a consequent increase in BMD, highlighting the specificity of this ligand-receptor pair for maintaining the formation, function, and survival of osteoclasts ([Dougall et al, 1999](#); [Kong et al, 1999a](#)).

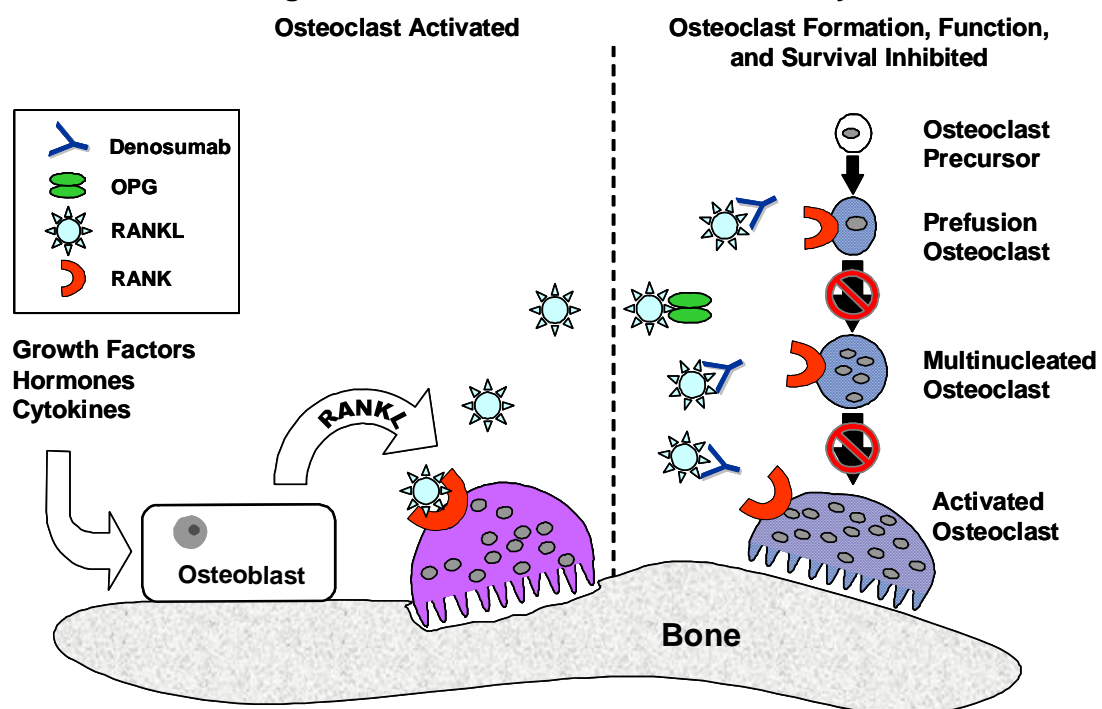
Osteoprotegerin (OPG) is the only known endogenous inhibitor of RANKL activity. OPG is a nonsignaling protein that functions as a soluble decoy receptor by binding to RANKL and thereby preventing the latter from activating RANK ([Simonet et al, 1997](#); [Kearns et al, 2008](#)). OPG production is increased by estrogen and by testosterone, an effect that likely contributes to the protective role of those sex hormones on bone ([Kearns et al, 2008](#)). Pharmacologic inhibition of RANKL by recombinant OPG or by denosumab significantly increased cortical and trabecular bone volume, density, and strength in numerous preclinical models of bone disease, including models of estrogen and androgen ablation ([Li et al, 2009](#); [Ominsky et al, 2008](#); [Ominsky et al, 2007](#)). Thus,

numerous lines of evidence suggest important roles for OPG and RANKL in regulating bone loss in pathological conditions, including bone loss associated with sex hormone ablation in males and in females.

3.3 Denosumab

The mechanism by which denosumab inhibits osteoclasts is similar or identical to that of OPG. Denosumab is a fully human IgG2 monoclonal antibody to RANKL that binds with high affinity and specificity to RANKL (K_d 3×10^{-12} M). This binding prevents the activation of RANK and inhibits the formation, function, and survival of osteoclasts (Figure 2), the result of which is a reduction in the number and function of osteoclasts and, consequently, a decrease in bone resorption and an increase in cortical and trabecular bone mass, volume, and strength (Kostenuik et al, 2009; Kostenuik, 2005). Denosumab is highly specific because it binds only to RANKL and does not bind to other members of the TNF family, including $TNF\alpha$, $TNF\beta$, TNF-related apoptosis-inducing ligand, or CD40 ligand (Kostenuik et al, 2009). As a result of its unique and specific mechanism of action, denosumab is being investigated as a therapy for PMO and bone loss associated with HALT, as well as other disease settings in which bone loss occurs. A brief timeline of RANKL pathway research and of denosumab development and clinical testing is provided in (Table 1).

Figure 2. The OPG/RANK/RANKL Pathway



Adapted from Boyle et al, 2003

Table 1. Timeline of RANK Ligand Pathway Research, Denosumab Development, and Clinical Testing in PMO and Bone Loss Due to HALT

1995 – 1998 Preclinical Data	RANK, RANKL, and OPG were cloned and their roles in regulating bone turnover were identified.	Anderson et al, 1997 Simonet et al, 1997 Lacey et al, 1998 Yasuda et al, 1998 Kong et al, 1999a Kong et al, 1999b Burgess et al, 1999
1999 – 2001 Denosumab Development	Amgen begins clinical trials of recombinant OPG protein. The first dose of denosumab was administered in humans on 30 June 2001.	Bekker et al, 2001 Bekker et al, 2004
2004 → Ongoing Denosumab Clinical Program	The phase 2 PMO BMD study demonstrated the biological activity of denosumab and identified 60-mg Q6M as the appropriate phase 3 dose. Phase 3 studies of denosumab demonstrated efficacy for the treatment and prevention of PMO and for the treatment and prevention of bone loss in patients undergoing hormone ablation for prostate or breast cancer. The denosumab BLA was filed with the FDA on 19 December 2008.	McClung et al, 2006 Body et al, 2006 Lipton et al, 2007 Ellis et al, 2008 Miller et al, 2008 Bone et al, 2008 Cummings et al, 2008 Brown et al, 2009

3.4 Denosumab Clinical Program in PMO and Bone Loss Due to HALT

The intent of Amgen's clinical development program in PMO and in bone loss due to HALT was to determine if denosumab's unique mechanism of action could deliver robust benefits to BMD and fracture risk at both vertebral and nonvertebral sites, with an acceptable safety profile, and with a dosing regimen that would be tolerable and likely to enhance long-term therapy and clinical effectiveness. Based on the data presented later in this document, we consider that the results of our extensive clinical trials met these goals.

The submitted Biologics License Application (BLA) contained data from 30 clinical studies ([Figure 3](#)) in normal volunteers and in patients with osteoporosis (approximately 10,500 subjects), bone loss associated with HALT (approximately 1700 subjects), rheumatoid arthritis, and advanced cancer performed from June 2001 to September 2008. Exposure to denosumab is summarized by years of exposure in [Figure 4](#).

Twelve studies were conducted in women with PMO or low BMD. Two studies were conducted in subjects with breast cancer or prostate cancer who had bone loss

associated with HALT (AIT and ADT, respectively); a third study in subjects with breast cancer receiving AIT is ongoing and remains blinded to treatment assignment. Nine additional studies provided biopharmaceutic and clinical pharmacology information as well as initial information on efficacy and tolerability of denosumab. The remaining 6 studies were conducted in patient populations outside the bone loss populations (ie, inhibition of structural damage in subjects with rheumatoid arthritis, prevention of skeletal-related events in subjects with advanced cancer and bone metastases, and treatment of multiple myeloma).

The PMO clinical development program is supported by 2 pivotal phase 3 studies (20030216 and 20040132) ([Table 2](#)). Study 20030216 was a 3-year randomized, double-blind, placebo-controlled study in postmenopausal women with osteoporosis to determine whether denosumab treatment could reduce the incidence of new vertebral fracture (primary endpoint) and of nonvertebral and hip fractures (secondary endpoints) (definitions of fracture categories are provided in [Appendix 2](#)). As this was a placebo-controlled trial, women were excluded if they had BMD T-scores < -4.0 at the lumbar spine or total hip, or any severe or more than 2 moderate prevalent vertebral fractures. If total hip BMD decreased $> 7\%$ during a 12-month period or by $\geq 10\%$ during the study, or the T-score decreased to < -4.0 during the study, the participant was counseled about alternative treatments in lieu of continuing the study treatments (subjects who discontinued treatment were encouraged to continue study observations). The trial and the process of informed consent were approved by institutional review boards overseeing the individual study sites. An ongoing, open-label, 7-year extension study (20060289) of the treatment of PMO fracture study (20030216) will provide data regarding long-term exposure to denosumab.

Study 20040132 was a 2-year, randomized, double-blind, placebo-controlled study in postmenopausal women with low BMD to determine whether denosumab treatment would prevent bone loss; this study also included a 2-year safety off-treatment follow-up phase.

Several other supportive phase 2 and phase 3 studies in PMO have been completed, including Studies 20010223, 20050141, and 20050234 ([Table 2](#)). Study 20010223 was a phase 2, randomized, double-blind, placebo-controlled, dose-ranging study in postmenopausal women with low BMD. Study 20050141 examined the effects of denosumab compared with alendronate on BMD and bone turnover markers in women not previously receiving bisphosphonate therapy. Study 20050234 examined the effects

of denosumab on BMD and bone turnover markers in women who switched from alendronate to denosumab therapy compared with women continuing to receive alendronate.

The HALT clinical development program is supported by 2 pivotal phase 3 studies (20040138 and 20040135) ([Table 2](#)). Study 20040138 is a randomized, double-blind, placebo-controlled study to determine the treatment effect of denosumab on bone loss in subjects receiving ADT for nonmetastatic prostate cancer. Study 20040138 also included prespecified endpoints for new vertebral and any fracture risk reduction. Study 20040135 is a randomized, double-blind, placebo-controlled study to determine the treatment effect of denosumab on bone loss in subjects receiving AIT for nonmetastatic breast cancer. Both studies include ongoing 2-year safety follow-up phases.

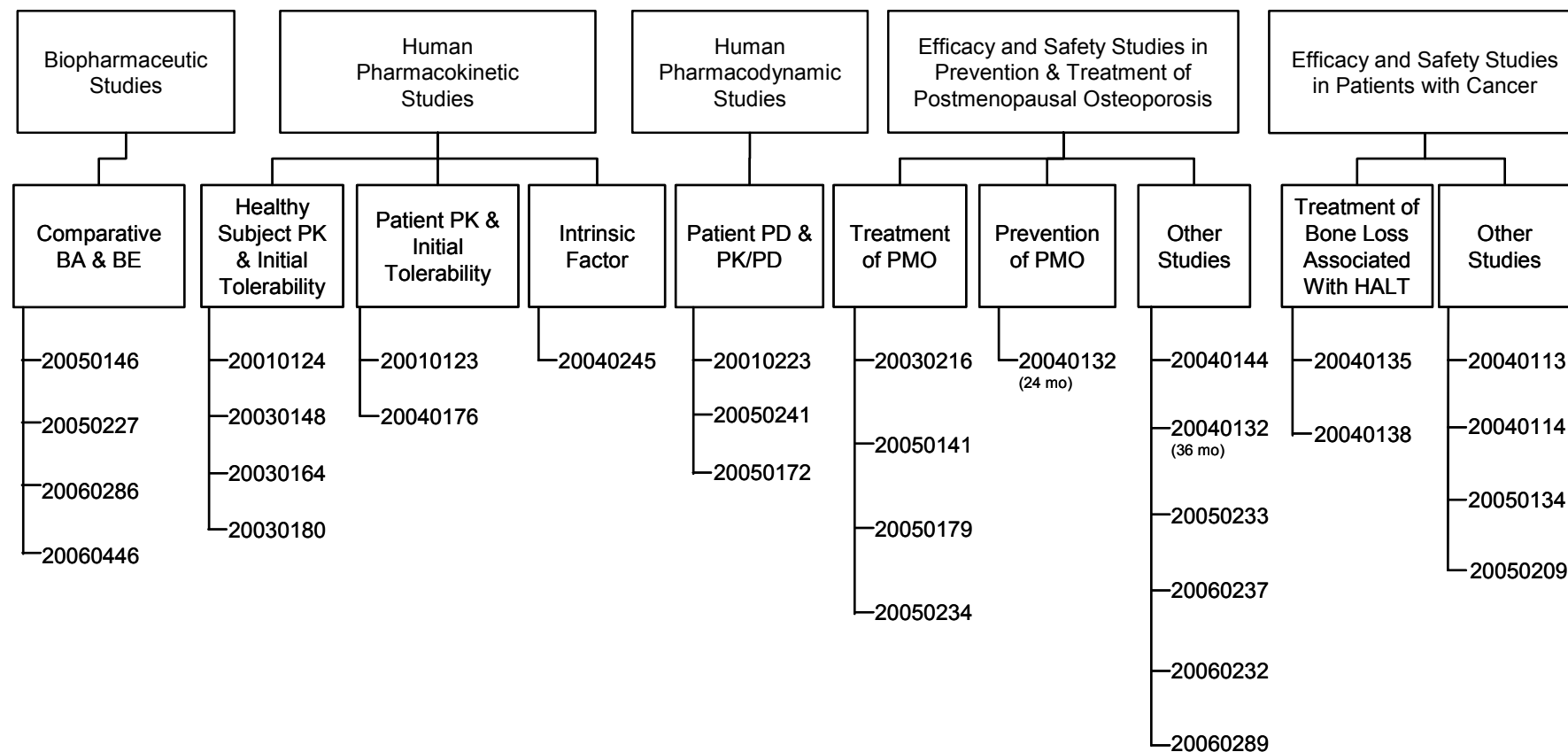
In all of the above phase 2 and 3 studies, patients received daily supplements containing calcium (at ≥ 1000 mg [except in study 20050141: ≥ 500 mg]) and vitamin D (≥ 400 IU).

Primary and secondary efficacy endpoints from the phase 3 studies are summarized in [Table 3](#). Details of statistical analyses are provided in [Appendix 3](#). Except as noted, all efficacy statistical analyses presented in this document were planned analyses.

Since denosumab study participants were all adults, no data were included in the application on the use of denosumab in pediatric subjects. Most subjects (85.4%) evaluated for safety were women (6686 denosumab, 4451 placebo), and 14.6% were men (1162 denosumab, 748 placebo). In the pivotal, placebo-controlled trials, most subjects of both sexes were ≥ 65 years old (PMO: 92%; HALT: 84%) and Caucasian (PMO: 82%; HALT: 85%). More than 1600 subjects of non-Caucasian ethnicities were included in denosumab studies (approximately 12% of all subjects).

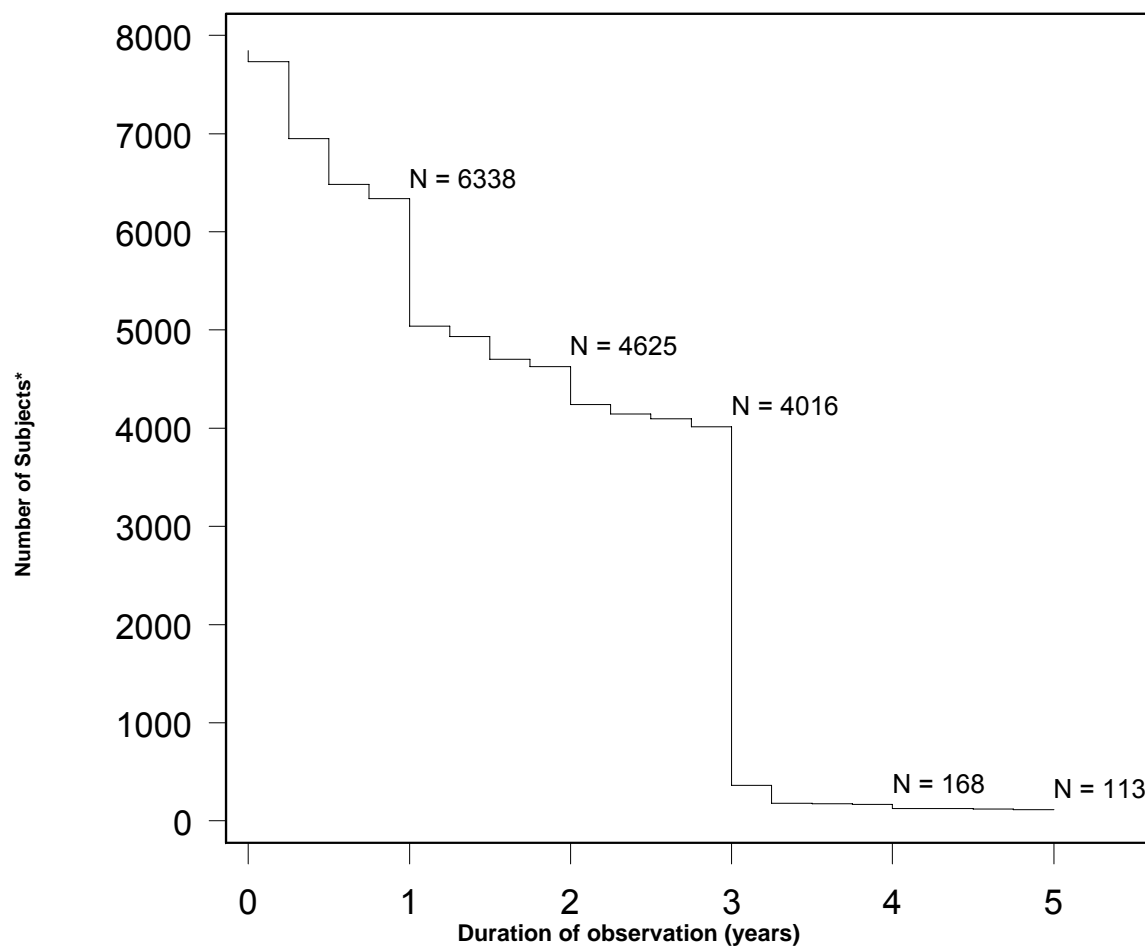
Most female subjects evaluated were postmenopausal. Pregnant or breastfeeding women were not eligible for enrollment in any denosumab clinical study. Women of childbearing potential and men enrolled in denosumab clinical studies were required to consent to practice an effective barrier method of contraception (eg, condoms/spermicide, intrauterine device) for the duration of their study participation.

Figure 3. Clinical Studies for the Denosumab Bone Loss BLA



BA = bioavailability; BE = bioequivalence; HALT = hormone ablation therapy; PD = pharmacodynamics; PK = pharmacokinetics; PMO = postmenopausal osteoporosis. Clinical studies were organized in the BLA per the Common Technical Document (CTD) structure which establishes the categories presented above. "Intrinsic factors" include age, sex, body composition, genetic polymorphism, and organ dysfunction.

Figure 4. Numbers of Subjects by Years of Denosumab Exposure (Overall Safety Analysis Set)



N = Number of subjects with denosumab exposure at the time point of interest

*The number of subjects with at least as much exposure as indicated on the x-axis.

Program: /stat/amg162/meta/bla_2008bone/analysis/rhdac/graphs/program/g_line_exp.sas

Output: g1-05_001_line_exp.cgm (Date Generated: 16JUN2009: 9:56:38)

Source Data: a08css.aslinfo

Table 2. Key Clinical Studies

Number	Study Design	Population	Primary Endpoint	Publications
20030216	Phase 3, randomized, double-blind, placebo-controlled Denosumab: 60 mg Q6M SC 3 yr treatment	7808 women with postmenopausal osteoporosis BMD T-score < -2.5 at the lumbar spine or total hip and not < -4.0 at either site Age: 60 to 90 yr	Incidence of new vertebral fractures over 3 yr	Cummings et al, 2008
20040132	Phase 3, randomized, double-blind, placebo-controlled Denosumab: 60 mg Q6M SC 2 yr treatment; 2 yr off-treatment follow-up	332 postmenopausal women with low BMD -2.5 ≤ T-score ≤ -1.0 at the lumbar spine Age: ≤ 90 yr	Percent change from baseline in lumbar spine BMD (by DXA) at 2 yr	Bone et al, 2008
20050141	Phase 3, randomized, double-blind, active-controlled (alendronate), double-dummy, parallel group Denosumab: 60 mg Q6M SC 1 yr treatment	1189 postmenopausal women with low BMD T-score ≤ -2.0 at the lumbar spine or total hip Age: open	Percent change from baseline in total hip BMD (by DXA) at 1 yr	Brown et al, 2009
20050234	Phase 3b, randomized, double-blind, active-controlled (alendronate), double-dummy, parallel group Denosumab: 60 mg Q6M SC 1 yr treatment	504 women with PMO who received alendronate 70 mg QW or equivalent for ≥ 6 mo before screening -4.0 ≤ T-score ≤ -2.0 at the lumbar spine or total hip Age: ≥ 55 yr	Percent change from baseline in total hip BMD (by DXA) at 1 yr	Kendler et al, 2008
20010223	Phase 2, randomized, double-blind, placebo-and active-controlled, dose-finding Denosumab: 6, 14, or 30 mg Q3M SC; or 14, 60, 100, or 210 mg Q6M SC Active control: alendronate 70 mg QW PO Up to 4 yr treatment	412 postmenopausal women with low BMD -4.0 ≤ T score ≤ -1.8 for lumbar spine or -3.5 ≤ T score ≤ -1.8 for total hip or femoral neck Age: ≤ 80 yr	Percent change from baseline in lumbar spine BMD (by DXA) at 1 yr	Miller et al, 2008

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ADT = androgen deprivation therapy; AIT = aromatase inhibitor therapy; BMD = bone mineral density; DXA = dual energy x-ray absorptiometry; PMO = postmenopausal osteoporosis; PO = orally; Q6M = every 3 months; Q6M = every 6 months; SC = subcutaneous

Table 2. Key Clinical Studies

Number	Study Design	Population	Primary Endpoint	Publications
20060289	Phase 3 open-label, single-arm, extension study Denosumab: 60 mg Q6M SC 7 yr treatment (total treatment duration 10 yr for subjects in the denosumab group of Study 20030216)	4550 women with postmenopausal osteoporosis who completed Study 20030216	Safety monitoring	None to date
20040138	Phase 3 randomized, double-blind, placebo-controlled Denosumab: 60 mg Q6M SC 3 yr treatment; 2 yr off-treatment follow-up	1468 men with nonmetastatic prostate cancer receiving ADT who were < 70 years of age and who had a history of osteoporotic fracture or a BMD T-score at the lumbar spine, total hip, or femoral neck < -1.0; men ≥ 70 years did not have to meet these latter requirements. Men with BMD-T scores of < -4.0 at lumbar spine, total hip, or femoral neck were excluded.	Percent change from baseline in lumbar spine BMD (by DXA) at 2 yr	Smith et al, 2009
20040135	Phase 3 randomized, double-blind, placebo-controlled Denosumab: 60 mg Q6M SC 2 yr treatment; 2 yr off-treatment follow-up	252 women with nonmetastatic breast cancer receiving AIT who had low BMD T-score of -1.0 to -2.5 at the lumbar spine, total hip, or femoral neck Age: ≥ 18 yr	Percent change from baseline in lumbar spine BMD (by DXA) at 1 yr	Ellis et al, 2008

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ADT = androgen deprivation therapy; AIT = aromatase inhibitor therapy; BMD = bone mineral density; DXA = dual energy x-ray absorptiometry; PMO = postmenopausal osteoporosis; PO = orally; Q6M = every 3 months; Q6M = every 6 months; SC = subcutaneous

Table 3. Primary and Secondary Efficacy Endpoints of Key Phase 3 Clinical Studies

Endpoint	PMO				HALT	
	Treatment of PMO Fracture (20030216)	Prevention of PMO (20040132)	Head-to-head vs Alendronate (Naive) (20050141)	Head-to-head vs Alendronate (Transition) (20050234)	HALT Breast Cancer (20040135)	HALT Prostate Cancer (20040138)
Fracture Endpoints						
Incidence of new vertebral fractures	Primary	–	–	–	–	Secondary
Time to first non-vertebral fracture	Secondary	–	–	–	–	–
Time to first hip fracture	Secondary	–	–	–	–	–
Incidence of any (osteoporotic) fracture	–	–	–	–	–	Secondary
Time to first clinical fracture	–	–	–	–	–	Secondary
BMD Endpoints, percent change from baseline in:						
Lumbar spine BMD	–	Primary	Secondary	Secondary	Primary	Primary
Total hip BMD	–	Secondary	Primary	Primary	Secondary	Secondary
Femoral neck BMD	–	Secondary	Secondary	–	Secondary	Secondary
Trochanter, 1/3 distal radius, and total body BMD	–	Secondary	Secondary	–	–	–
Trabecular, cortical, and total volumetric BMD of the distal radius	–	Secondary	–	–	–	–
Bone Turnover Marker Endpoint						
Percent change from baseline in serum type 1 C-telopeptide (CTX1)	–	–	–	Secondary	–	–

Note: Tests involving primary and secondary endpoints were controlled for multiplicity ([Appendix 3](#)).

3.5 Proposed Indications

Table 4. Proposed Indications for Denosumab, 60 mg SC Q6M

Treatment of osteoporosis in postmenopausal women
Prevention of osteoporosis in postmenopausal women
Treatment and prevention of bone loss associated with hormone ablation therapy with breast cancer
Treatment and prevention of bone loss associated with hormone ablation therapy in patients with prostate cancer

3.6 Future Indications: Treatment of Bone Metastases in Advanced Cancer

Bone metastases and their clinical sequelae are among the most frequent debilitating complications in patients with advanced cancer and are particularly evident in the settings of breast and prostate cancer. RANKL increases osteoclast activity in patients with advanced malignancies involving bone. Denosumab has been shown to reduce bone resorption and cancer-induced bone destruction in animal models. Therefore, denosumab is being investigated as a therapy to prevent bone complications in patients with advanced cancer, including occurrence of skeletal-related events (ie, pathological fracture, radiation to bone, spinal cord compression, or surgery to bone) and to prevent or delay bone metastases in patients with prostate cancer at risk for bone metastases.

Denosumab is also being investigated for the treatment of giant cell tumor of the bone, a rare, aggressive, usually benign, but potentially malignant tumor that presents as an eccentric osteolytic lesion, usually in the epiphyses of long bones. The studies supporting the ongoing clinical program in advanced cancer settings are outlined in [Table 5](#). These studies are planned to support additional future indications for denosumab.

Table 5. Ongoing Clinical Program for Denosumab in Advanced Cancer Settings

Study	Study Design	Study Population	Primary Objective
<u>Advanced Malignancies Involving Bone</u>			
20050136	Phase 3, randomized, double-blind, active-controlled Denosumab: 120 mg Q4W SC Zoledronic acid: 4 mg Q4W IV	2049 adults (men included) with histologically or cytologically confirmed breast adenocarcinoma; current or prior radiographic evidence of at least 1 bone metastasis	To determine if denosumab is noninferior to zoledronic acid with respect to the first on-study occurrence of an SRE
20050244	Phase 3, randomized, double-blind, active-controlled Denosumab: 120 mg Q4W SC Zoledronic acid: 4 mg Q4W IV	1779 adults with histologically or cytologically confirmed advanced cancers including solid tumors (except breast and prostate cancer), multiple myeloma, and lymphoma; current or prior radiographic evidence of at least 1 bone metastasis (or lytic bone lesion from multiple myeloma)	To determine if denosumab is noninferior to zoledronic acid with respect to the first on-study occurrence of an SRE
20050103	Phase 3, randomized, double-blind, active-controlled Denosumab: 120 mg Q4W SC Zoledronic acid: 4 mg Q4W IV	1904 adult men with histologically-confirmed prostate cancer; current or prior radiographic evidence of at least 1 bone metastasis	To determine if denosumab is noninferior to zoledronic acid with respect to the first on-study occurrence of an SRE
<u>Prevention of Bone Metastases</u>			
20050147	Phase 3, randomized, double-blind, placebo-controlled Denosumab: 120 mg Q4W SC	1436 adult men with histologically-confirmed prostate cancer who are at high risk for developing bone metastases; no current or prior radiographic evidence of bone metastasis	To compare the treatment effect of denosumab with placebo on prolonging bone metastasis-free survival.

Page 1 of 2

IV = intravenous; Q4W = every 4 weeks; SC = subcutaneous; SRE = skeletal-related event (composite endpoint that includes fractures, radiation to bone, spinal cord compression, and surgery to bone)

Table 5. Ongoing Clinical Program for Denosumab in Advanced Cancer Settings

Study	Study Design	Study Population	Primary Objective
<u>Treatment of Giant Cell Tumor of the Bone</u>			
20040215	Phase 2, open-label Denosumab 120 mg SC on days 1, 8, 15, 29 and Q4W thereafter	37 adults with pathologically confirmed giant cell tumor of the bone	To evaluate response to treatment
20062004	Phase 2, open-label Denosumab 120 mg SC on days 1, 8, 15, 29 and Q4W thereafter	61 adults with pathologically confirmed giant cell tumor of the bone	To evaluate safety

Page 2 of 2

IV = intravenous; Q4W = every 4 weeks; SC = subcutaneous; SRE = skeletal-related event
(composite endpoint that includes fractures, radiation to bone, spinal cord compression, and
surgery to bone)

4. Dose Regimen in PMO and Bone Loss Associated With HALT

4.1 Key Points

- The 60 mg Q6M dose regimen was the lowest dose at the least frequent interval that resulted in maximal bone mineral density (BMD) gains across skeletal sites.
- Patient preference for a Q6M subcutaneous (SC) injection over a QW oral (PO) tablet, which was demonstrated in 2 head-to-head studies comparing denosumab to alendronate, may contribute to patient adherence and clinical outcomes.

4.2 Dose Rationale

The selection of the 60 mg SC Q6M dose regimen for the phase 3 studies of denosumab in PMO and bone loss associated with HALT was based on data from a dose-ranging phase 2 study (20010223) conducted in postmenopausal women with low BMD. This dosing regimen was the least frequent interval that would provide the maximal gains in BMD. A less frequent dosing interval was selected because it may provide benefit to patients with respect to greater treatment adherence. This dosing regimen was also supported by phase 1 data indicating similar pharmacokinetic and pharmacodynamic characteristics for denosumab in the proposed patient populations. The safety and tolerability profile was comparable to placebo for all dose regimens evaluated in phase 1 studies, as well as in the phase 2 dose-ranging study (20010223).

In Study 20010223, Q3M doses of 6, 14, and 30 mg and Q6M doses of 14, 60, 100, and 210 mg were evaluated. All doses evaluated provided similar maximal reductions in serum CTX1, but there were differences in the duration of maximal effects ([Figure 5](#); data for 6 and 14 mg Q3M doses not shown). The 6 and 14 mg Q3M dose regimens did not provide adequate overall suppression of bone resorption, based on lower gains in BMD across anatomical sites, and these regimens were thus not considered for the phase 3 studies. The 30 mg Q3M and 100 and 210 mg Q6M dose regimens resulted in the maintenance of maximal reductions in serum CTX1 over the 3- or 6-month dosing intervals ([Figure 5](#)). Although the 60 mg Q6M dose regimen demonstrated mild attenuation at the end of the dosing interval, the gain in total hip BMD at 24 months for the 60 mg dose was comparable to that observed for the 30 mg Q3M and 100 and 210 mg Q6M doses ([Figure 6](#)). Hence, 60 mg was the lowest dose at the Q6M interval that resulted in maximal BMD gains, with a safety and tolerability profile similar to placebo.

Figure 5. Median Percent Change from Baseline for Serum CTX1 in Postmenopausal Women With Low BMD Administered Various Denosumab Dose Regimens (Phase 2 Dose-Ranging Study [20010223])

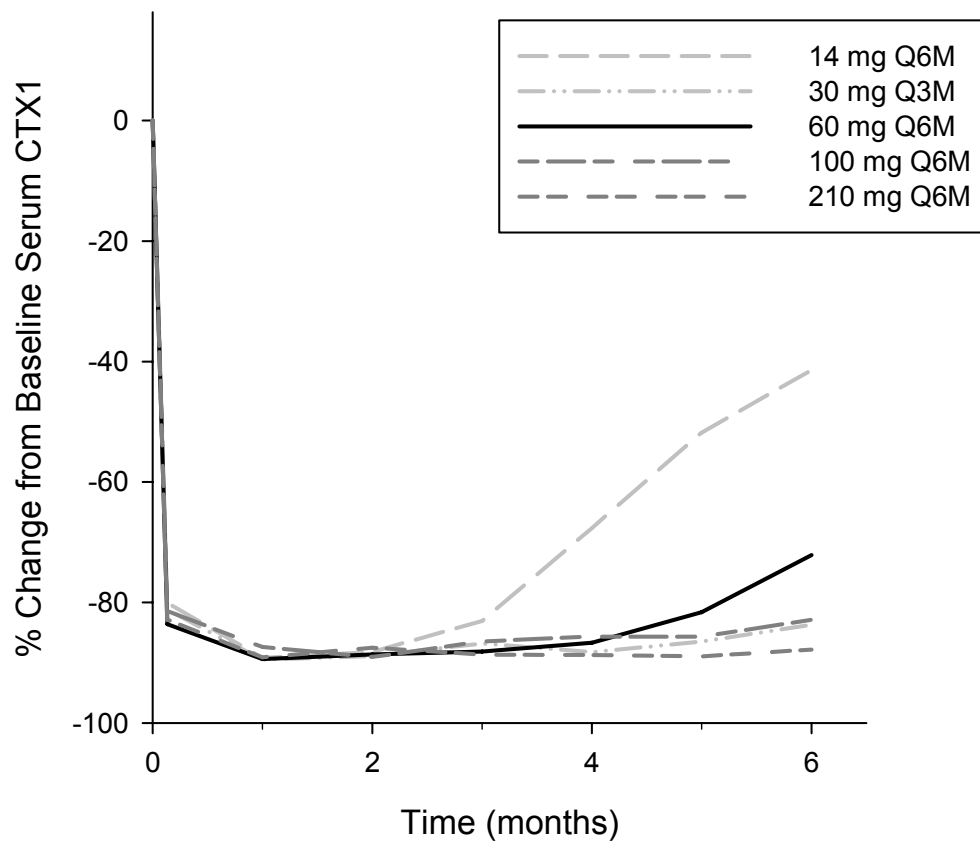
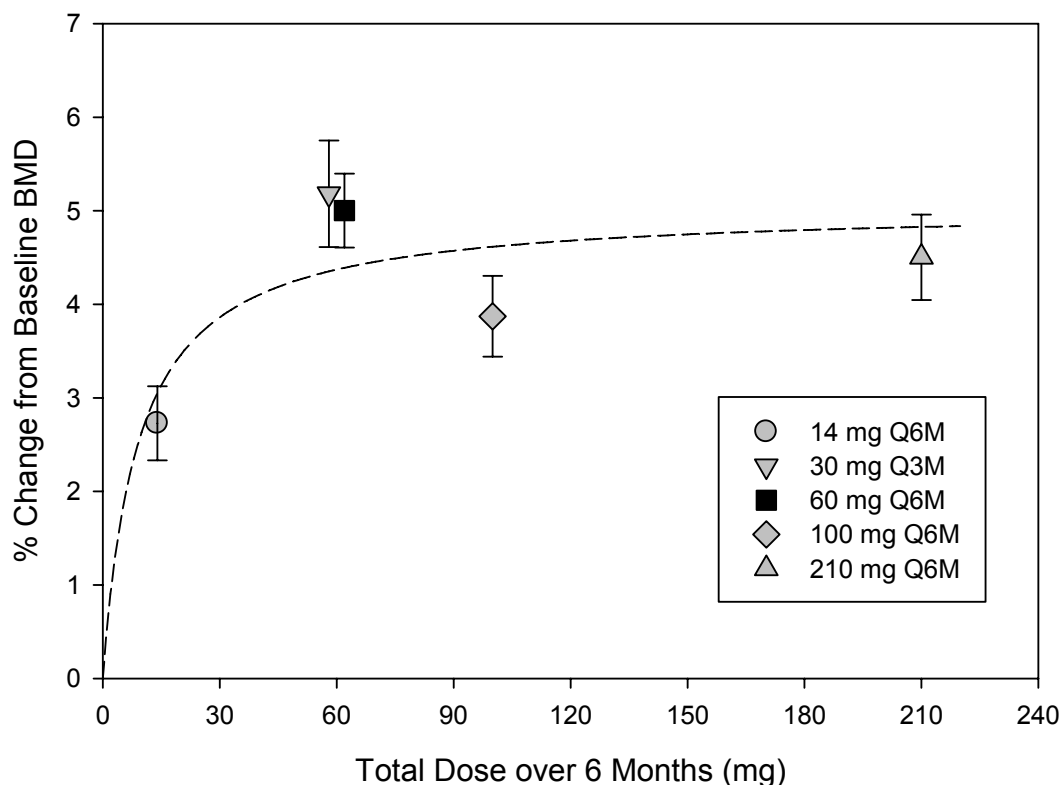


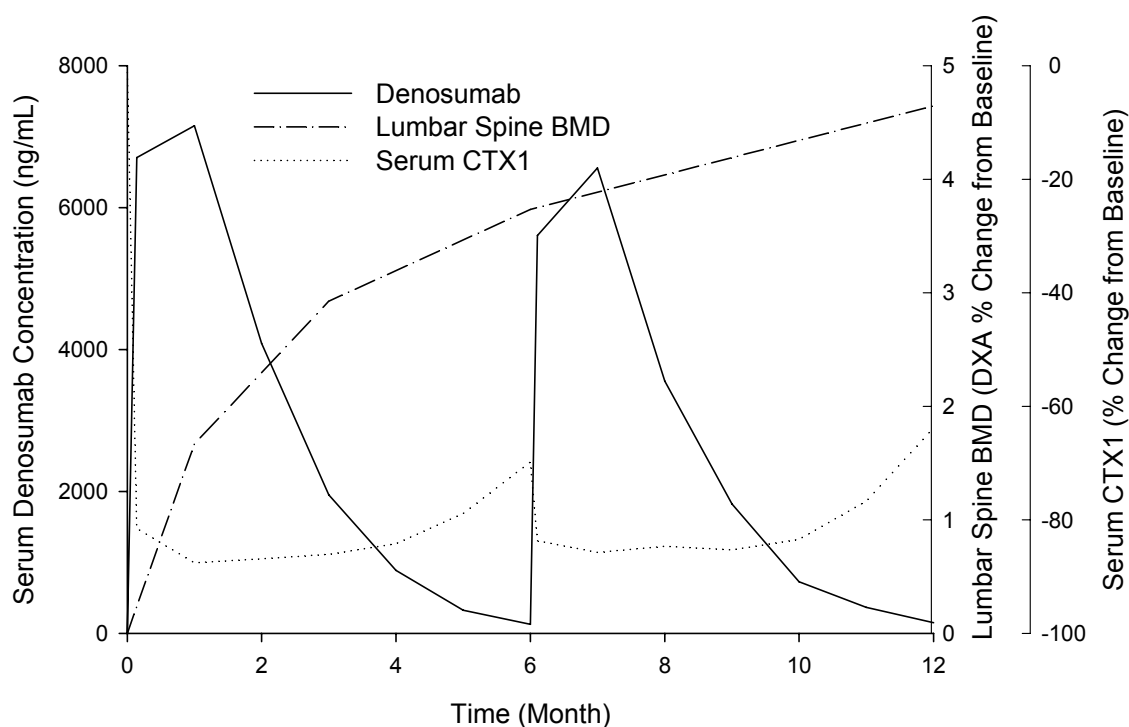
Figure 6. Mean (SEM) Percent Increase From Baseline to 24 Months in Total Hip BMD in Postmenopausal Women with Low BMD Administered Various Denosumab Dose Regimens (Phase 2 Dose-ranging Study [20010223])



The pharmacokinetic and pharmacodynamic characteristics of denosumab support the effectiveness of this extended dosing regimen and the reversibility of denosumab pharmacodynamic effects. Following SC administration, 61% of the administered dose reaches the systemic circulation, which is typical for a monoclonal antibody ([Mascelli et al, 2007](#)). Denosumab has a volume of distribution similar to that of other antibodies, and preclinical data indicate that it is not bound or sequestered in bone. Denosumab is cleared from the body by mechanisms shared with other IgG, including internalization by cells of the reticulo-endothelial system and catabolism to its protein components. The neonatal Fc receptor (FcRn) protects IgG from this catabolism ([Roopenian and Akilesh, 2007](#)), resulting in the slow clearance of denosumab and a half-life of 26 days (which is similar to that of other antibodies [[Xolair® Prescribing Information](#)]). The overall rate of elimination of denosumab is also similar to that of other monoclonal antibodies and is markedly slower than the rates typically observed for small molecule drugs. These pharmacokinetic attributes of denosumab contribute to serum exposures for a 60 mg SC dose that are measurable over most of the 6-month dosing interval ([Figure 7](#)). The pharmacokinetic attributes are further reflected in the pharmacodynamic characteristics

in that bone turnover is suppressed over the 6-month dose interval, with significant gains in BMD. For this dose, the slight attenuation in the reduction in serum CTX1 at the end of the dose interval reflects the reversibility of denosumab PD effects as serum denosumab levels diminish ([Figure 7](#)).

Figure 7. Mean Serum Denosumab Concentration and Mean Percent Changes from Baseline for Serum CTX1 and Lumbar Spine BMD Following Two 60-mg Q6M Doses of Denosumab to Postmenopausal Women with Low BMD (Phase 2 Study [20010223])



4.3 Subject Preference for Q6M Dosing

Two head-to-head studies compared denosumab (60 mg Q6M SC) to alendronate (70 mg QW PO) in women with PMO (Studies 20050141 and 20050234) ([Table 2](#)).

These studies featured a double-dummy design such that subjects experienced both the SC and PO regimens but did not know which regimen included an active agent; this design allowed for an unbiased assessment of subjects' preferences between these regimens. These studies demonstrated that, among subjects reporting a preference, > 75% preferred a Q6M SC injection to a weekly oral tablet.

Although differences in adherence were not observed in the clinical trial setting, a greater preference for SC injection once every 6 months may contribute to adherence to therapy.

5. Clinical Efficacy of Denosumab for the Treatment and Prevention of PMO

5.1 Key Points

- The clinical development program in PMO is supported by the following key studies:
 - Pivotal, phase 3, treatment of PMO fracture study (20030216) (n = 7808)
 - Pivotal, phase 3, prevention of PMO study (20040132) (n = 332)
 - Phase 3, head-to-head vs alendronate (naive) study (20050141) (n = 1189)
 - Phase 3, head-to-head vs alendronate (transition) study (20050234) (n = 504)
 - Phase 2, dose-ranging study (20010223) (n = 412)
- Denosumab statistically significantly reduced the risk (compared with placebo) of new vertebral fractures by 68%, nonvertebral fractures by 20%, and hip fractures by 40%. Significant vertebral fracture reduction was observed at 1 year and was sustained for 3 years. Open-label data will be collected for up to 10 years of total exposure to denosumab.
- Consistent with denosumab's mechanism of action, bone turnover markers and histomorphometric parameters showed findings consistent with decreased bone remodeling.
- Denosumab significantly increased BMD at all skeletal sites measured.
- In 2 active-controlled studies, BMD increases were significantly greater than those observed with alendronate.
- Increases in BMD and decreases in bone turnover markers due to denosumab treatment were reversible upon discontinuation of denosumab therapy.
- Bone histology in denosumab-treated subjects showed that bone was of normal quality.

5.2 Demographics and Disposition in PMO Phase 3 Studies

In the treatment of PMO fracture study (20030216), mean age (72.3 years), time since menopause (24.2 years), and mean lumbar spine BMD T-score (-2.83) ([Table 6](#)) were consistent with the eligibility criteria (postmenopausal women with BMD T-score at the lumbar spine or total hip < -2.5 and ≥ -4.0). Women enrolled in prevention of PMO study (20040132) were younger (mean age: 59.4 years) and had higher lumbar spine BMD (mean T-score: -1.6), consistent with the enrollment criteria for this study (postmenopausal women with low bone mass and lumbar spine BMD T-score between -1.0 and -2.5).

The head-to-head vs alendronate studies (20050141 and 20050234) both enrolled women with BMD T-scores ≤ -2.0 at the lumbar spine and/or the hip. Consequently, key demographics in these 2 supportive, phase 3 studies were similar with respect to age, time since menopause, and baseline BMD T-scores (Table 6). The 2 studies differed in that subjects in Study 20050141 were generally treatment-naïve upon study entry (12% had prior use of bisphosphonates) whereas all subjects (100%) in Study 20050234 had substantial use of bisphosphonates upon study entry (> 6 months and median of 3 years). Among the denosumab studies summarized here, the substantial prior use of bisphosphonates is unique to Study 20050234.

Table 6. Summary of Demographics and Disposition of Phase 3 PMO Studies

	Phase 3, Treatment of PMO Fracture (20030216)	Phase 3, Prevention of PMO (20040132)	Phase 3, Head- to-head vs Alendronate (Naïve) (20050141)	Phase 3, Head- to-head vs Alendronate (Transition) (20050234)
n	7808	332	1189	504
% Women	100%	100%	100%	100%
% White	93%	83%	84%	93%
Mean (SD) age (years)	72.3 (5.2)	59.4 (7.5)	64.4 (8.5)	67.6 (7.8)
Mean (SD) BMD T-score at the lumbar spine	-2.83 (0.69)	-1.6 (0.42)	-2.57 (0.75)	-2.63 (0.77)
Mean (SD) years since menopause	24.2 (7.5)	10.0 (8.9)	17.1 (10.0)	19.3 (9.6)
% Prevalent vertebral fractures at baseline ^a	24%	3%	5%	9%
Median (range) of prior bisphosphonate treatment (months)	N/A	N/A	N/A	36.0 (6 – 192)
% Completed Study	83%	86% ^b	94%	95%

N/A = not applicable

^a Based on radiographic assessments for Study 20030216 and on medical history for other studies.

^b Completion of the 2-year treatment period

Source: Clinical Study Reports (CSRs) for studies 20030216, 20040132 (24-month), 20050141, and 20050234

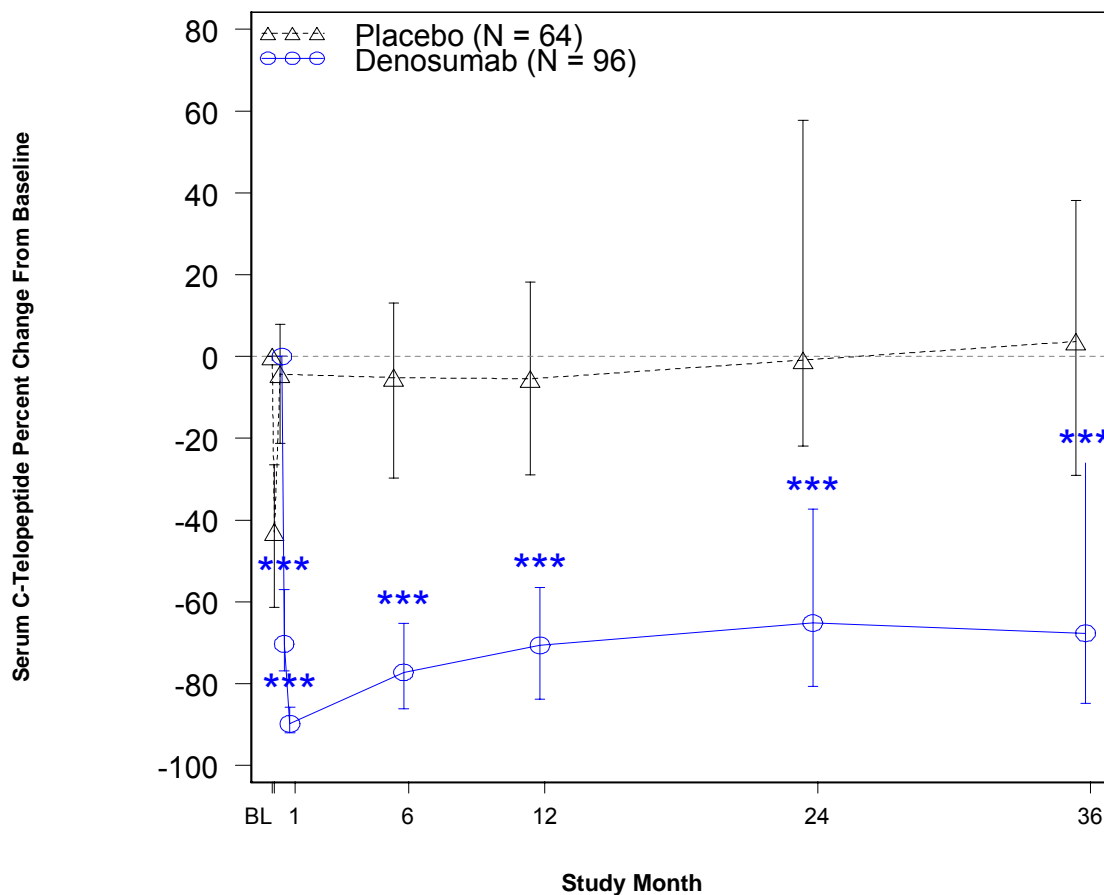
5.3 Denosumab Effects on Bone Turnover Markers

Consistent with its mechanism of action, denosumab decreased bone turnover as measured by markers of bone resorption (serum CTX1; [Figure 8](#)) and bone formation (intact N-terminal propeptide of type 1 procollagen [P1NP]; [Figure 9](#)) relative to placebo. As expected, decreases in markers of bone formation occurred after the decreases in bone resorption markers, consistent with the primary effect of denosumab, ie, inhibition of osteoclast activity. This observation suggests that coupling between bone formation and bone resorption was maintained during denosumab treatment.

Decreases in bone resorption markers observed for subjects receiving denosumab occurred as early as 6 hours postdose for serum CTX1, with maximal reductions observed at month 1 (90% [median] decrease at month 1 for serum CTX1 in the treatment of PMO fracture study [20030216]). Although serum CTX1 remained significantly reduced prior to the next dose (> 60% [median] decrease at month 6 and subsequent predose time points), a small attenuation of effect was observed at the end of the dosing interval ([Section 4.2](#)), reflecting reversibility of denosumab's effects on bone as serum levels of denosumab diminished. This dynamic profile is a characteristic of denosumab and has been observed across studies.

Thus, the effect of denosumab on bone turnover markers was rapid, sustained, and (as discussed further in [Section 5.6](#)) reversible.

**Figure 8. Serum CTX1 Percent Change From Baseline
(Median and Inter-Quartile Range) in Treatment of PMO Fracture Study
(Study 20030216; Randomized Subjects Enrolled in the Bone Marker Substudy)**



N = Number of randomized subjects enrolled in the bone marker substudy

* statistically significant (p-value ≤ 0.05); ** statistically significant (p-value ≤ 0.025);

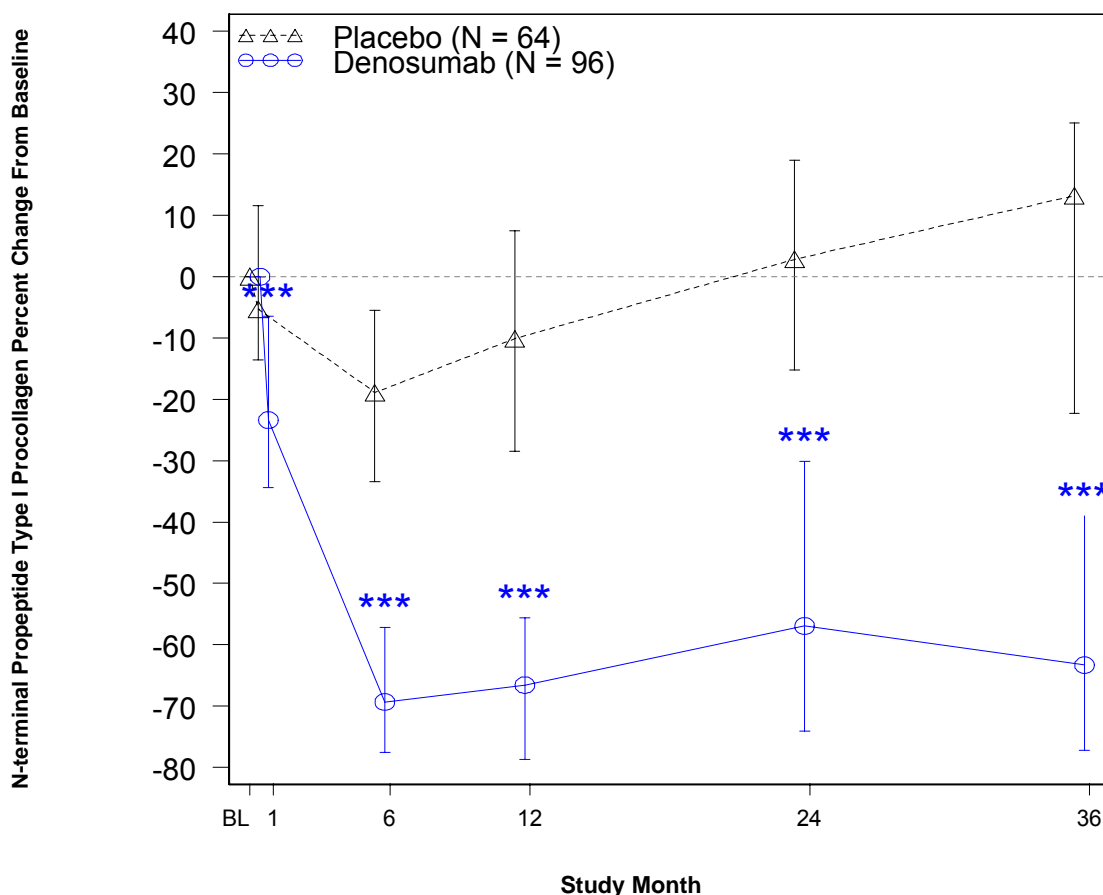
*** statistically significant (p-value ≤ 0.01)

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Source Data: adam.aslinfo, adam.albns

**Figure 9. P1NP Percent Change From Baseline
(Median and Inter-Quartile Range) in Treatment of PMO Fracture Study
(Study 20030216; Randomized Subjects Enrolled in the Bone Marker Substudy)**



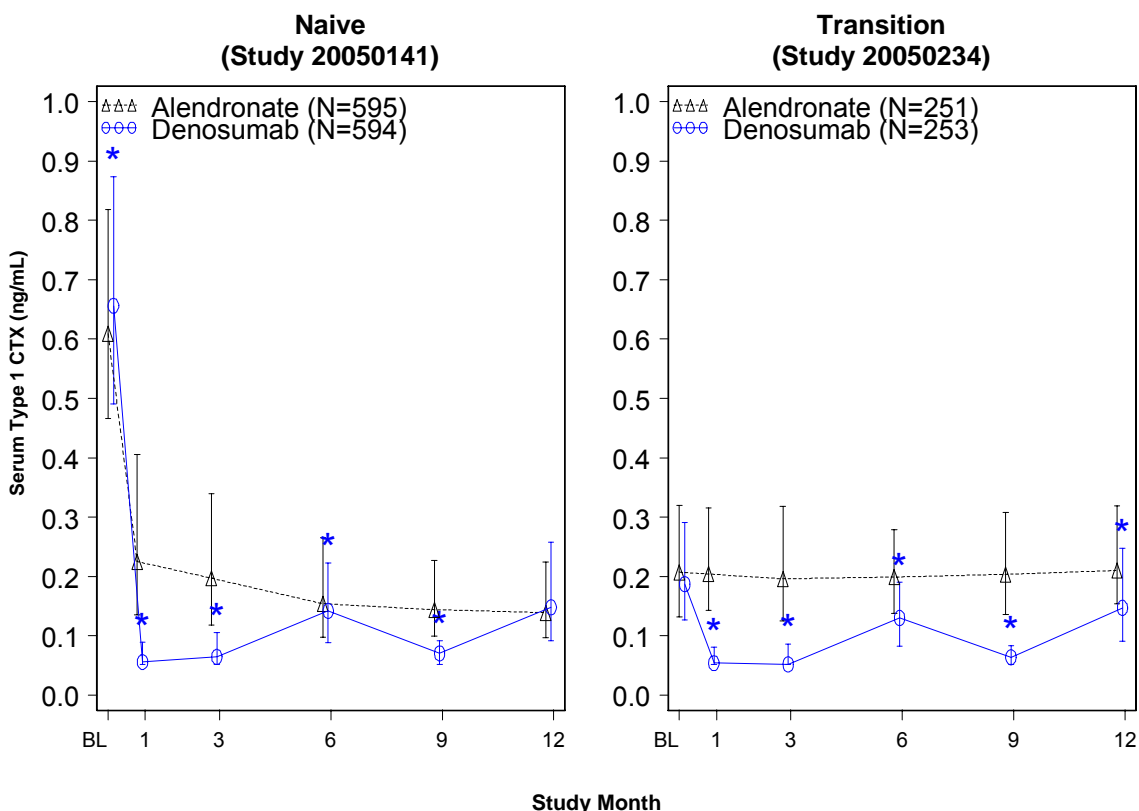
N = Number of randomized subjects enrolled in the bone marker substudy
* statistically significant (p-value ≤ 0.05); ** statistically significant (p-value ≤ 0.025);
*** statistically significant (p-value ≤ 0.01)

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Source Data: adam.aslinfo, adam.albbns

The observation of attenuation in reduction in serum CTX1 at the end of the dose interval contrasts with findings in treatment-naïve subjects treated with alendronate (Study 20050141). In that study, no attenuation in serum CTX1 was observed in the alendronate group, while slight attenuation was observed in the denosumab group, consistent with other studies (Figure 10). Alendronate has strong affinity for hydroxyapatite and accumulates in bone matrix; consequently, its effects can be sustained for months to years after treatment with alendronate is discontinued (Russell et al, 2007). In subjects with significant prior exposure to alendronate (70 mg QW or equivalent for ≥ 6 months before screening), transition from alendronate to denosumab resulted in additional and significant decreases in bone turnover markers (head-to-head

study vs alendronate transition study [20050234]). Thus, the effect of denosumab on bone markers was rapid and sustained, regardless of subjects' prior use of bisphosphonates. In subjects treated with denosumab, serum CTX1 concentrations were similar in subjects receiving denosumab for the first time (Study 20050141) and in subjects transitioning from alendronate therapy (Study 20050234) (Figure 10).

Figure 10. Serum CTX1 Concentration (Median and Inter-Quartile Range) in Head-to-head vs Alendronate Studies (Observed Data Subset)



N = Number of subjects randomized

* Indicates significance after multiplicity adjustment at a 5% level P-value based on Wilcoxon rank-sum test and van Elteren stratified test (adjusting for length of prior alendronate stratification variable) f

studies 20050141 and 20050234, respectively

P-values for study 20050141 are adjusted for multiple comparisons using Hochberg's procedure.

Program: /stat/amg162/meta/bla_2008bone/analysis/rhdac/graphs/program/g_line_ctx.sas

Output: g1-04_006_001_line_ctx_141_234.cgm (Date Generated: 12JUN2009:16:01:53)

Source Data: a050141.aslinfo, a050141.albbns, a050234.aslinfo, a050234.albbns

Denosumab decreased bone turnover markers to a greater degree than alendronate (Figure 10), which may be a reflection of the different mechanisms of action.

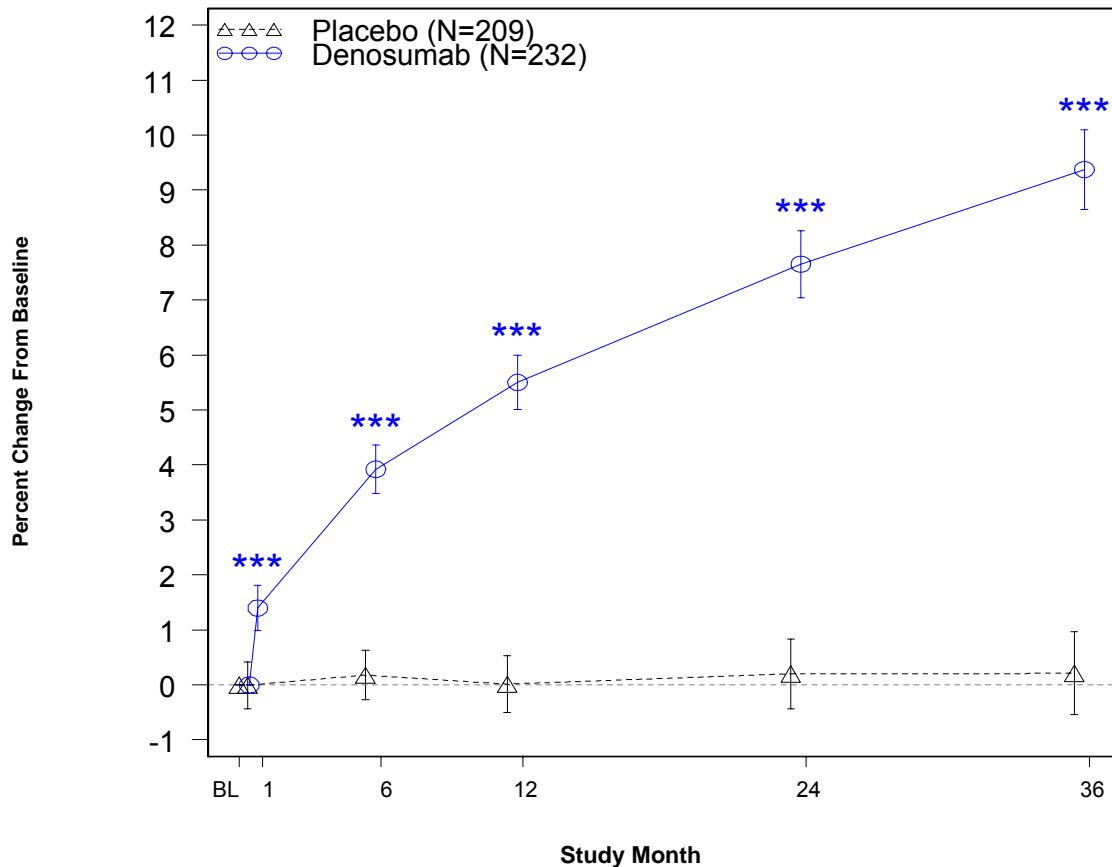
Alendronate and other bisphosphonates bind with high affinity to bone matrix and are subsequently taken up by mature osteoclasts during bone resorption, leading to osteoclast apoptosis and disruption of their bone-resorbing capability (Russell et al,

2007). Bisphosphonates therefore concentrate their action only in areas of the skeleton undergoing rapid bone turnover. In contrast, denosumab, by inhibiting RANKL, not only inhibits the activity of mature osteoclasts, but also inhibits differentiation of pre-osteoclasts and osteoclast survival (Figure 2).

5.4 Denosumab Effects on BMD

In all studies supporting efficacy, denosumab yielded statistically significant increases in BMD of the lumbar spine, total hip, femoral neck, hip trochanter, distal 1/3 radius, and total body (without head) compared with placebo or alendronate. Increases in BMD were observed as early as 1 month after the initial dose at the lumbar spine (Figure 11), total hip, and hip trochanter (only these skeletal sites were assessed at 1 month). Statistically significant increases were observed in both predominantly trabecular and predominately cortical bone sites.

Figure 11. Lumbar Spine BMD (by DXA): Percent Change From Baseline by Visit – Least-squares Mean and 95% CIs From ANCOVA Treatment of PMO Fracture Study (20030216) (Primary Efficacy Analysis Set in the DXA Substudy, LOCF)



N = Number of subjects enrolled in the DXA substudy

Point estimates and nominal 95% confidence intervals are based on an ANCOVA model adjusting for treatment, baseline value, machine type, and baseline value-by-machine type interaction.

* statistically significant (p-value ≤ 0.05), ** statistically significant (p-value ≤ 0.025),

*** statistically significant (p-value ≤ 0.01)

Source: 20030216 CSR

In the treatment of PMO fracture study (20030216), 95% of subjects receiving denosumab and 53% of subjects receiving placebo, had increases in lumbar spine BMD (change from baseline to month 36 $> 0\%$) (Table 7). Increases in lumbar spine BMD from baseline to month 36 that were $> 3\%$ were observed in 90% of subjects receiving denosumab and 30% of subjects receiving placebo.

Table 7. Subject Incidence of Lumbar Spine BMD Percent Change From Baseline ≤ 0 , > 0 to ≤ 3 , > 3 to ≤ 6 , and $> 6\%$ at Month 36 in the Treatment of PMO Fracture Study (20030216) (Primary Efficacy Analysis Set, LOCF)

	N1	Levels of BMD Response			
		$\leq 0\%$ n (%)	> 0 to 3% n (%)	$> 3\%$ to 6% n (%)	$> 6\%$ n (%)
Placebo (N = 3906)	3160	1473 (47)	736 (23)	548 (17)	403 (13)
Denosumab 60 mg Q6M (N = 3902)	3203	145 (5)	179 (6)	426 (13)	2453 (77)

N = Number of subjects randomized. N1 = Number of subjects with an evaluation during the time point of interest. Percentages are based on N1.

Source: 20030216 CSR

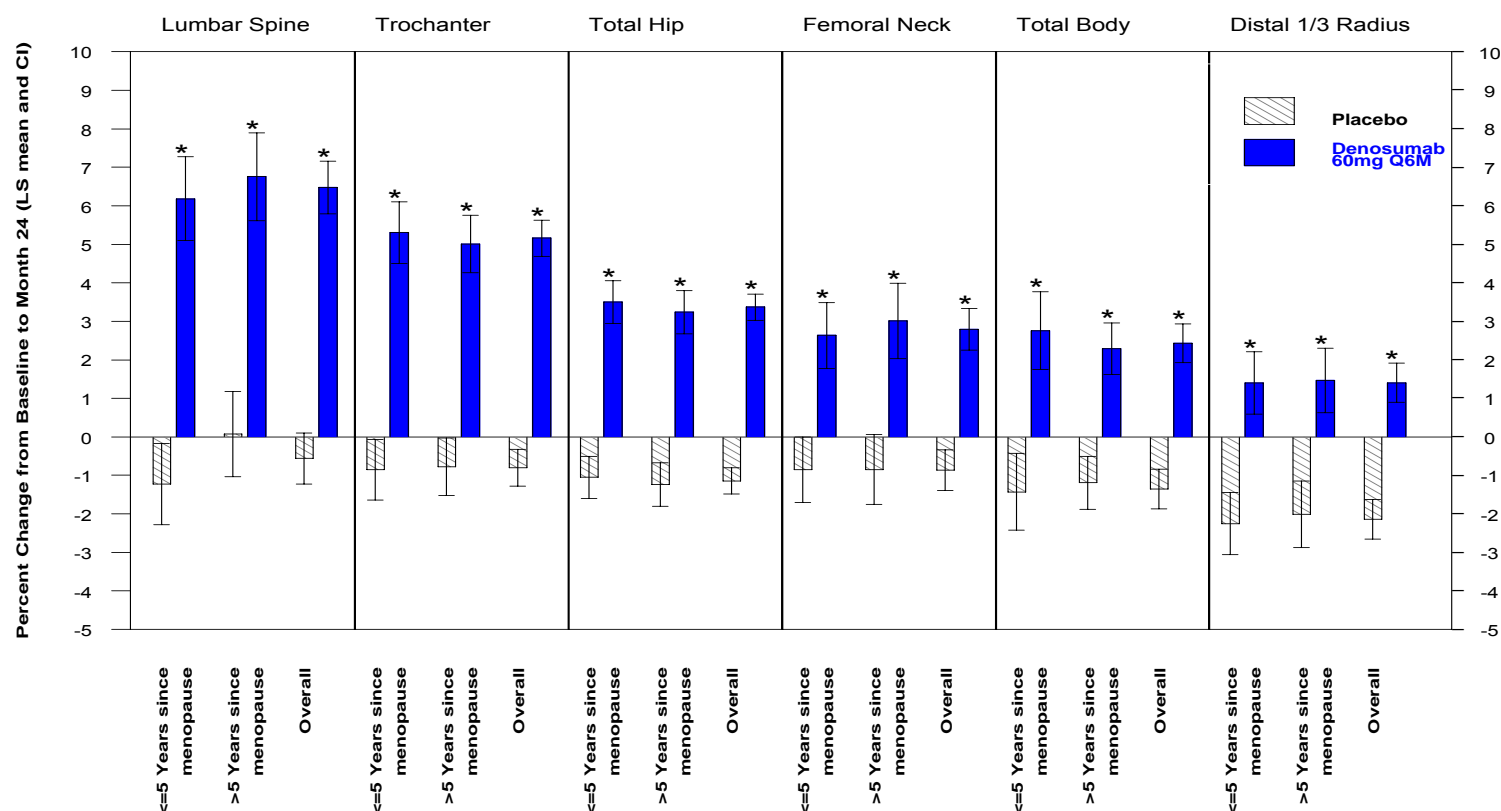
In the treatment of PMO fracture study (20030216), denosumab increased lumbar spine BMD by 8.8%, total hip BMD by 6.4%, femoral neck BMD by 5.2%, and hip trochanter BMD by 8.3% over 3 years, relative to placebo (all $p < 0.0001$). In a substudy, denosumab increased distal 1/3 radius BMD by 3.5%, and total body BMD by 4.1% over 3 years, relative to placebo (both $p < 0.0001$).

In the treatment of PMO fracture study (20030216), lumbar spine and total hip BMDs were obtained at baseline and month 36 for most subjects, which permitted robust subgroup analyses. Denosumab significantly increased BMD from baseline to month 36 in all subgroups of baseline characteristics examined (subgroups of age, geographic region, body weight, BMI, lumbar spine BMD T-score, total hip BMD T-score, serum CTX1 and kidney function based on creatinine clearance levels). Thus, denosumab increased BMD across a broad population of women with PMO.

The prevention of PMO study (20040132) in women with low BMD (lumbar spine BMD T-score of -1.0 to -2.5) provided further evidence for the effect of denosumab on BMD at all skeletal sites. Denosumab increased lumbar spine BMD by 7.0%, total hip BMD by 4.5%, femoral neck BMD by 3.7%, hip trochanter BMD by 6.0%, distal 1/3 radius by 3.5%, and total body BMD by 3.8% over 2 years, relative to placebo (all $p < 0.0001$) (Figure 12). Change in BMD at the lumbar spine was the primary endpoint for this study; changes in BMD at the other skeletal sites were secondary endpoints (Table 3).

As demonstrated in head-to-head studies, denosumab significantly increased BMD at all skeletal sites to a greater extent than did alendronate, both in women who were treatment naive to bisphosphonate therapy (Study 20050141) and in women with substantial prior exposure to alendronate who transitioned to denosumab (Study 20050234) (Figure 13). The increases in BMD at each skeletal site were higher in the treatment-naive study (20050141).

Figure 12. Bone Mineral Density by DXA: Percent Change From Baseline to Month 24 in Prevention of PMO Study (20040132), Month 24 Analysis – End of Treatment Period (Least-squares Means and CIs From ANCOVA Model; Primary Efficacy Subset, LOCF)

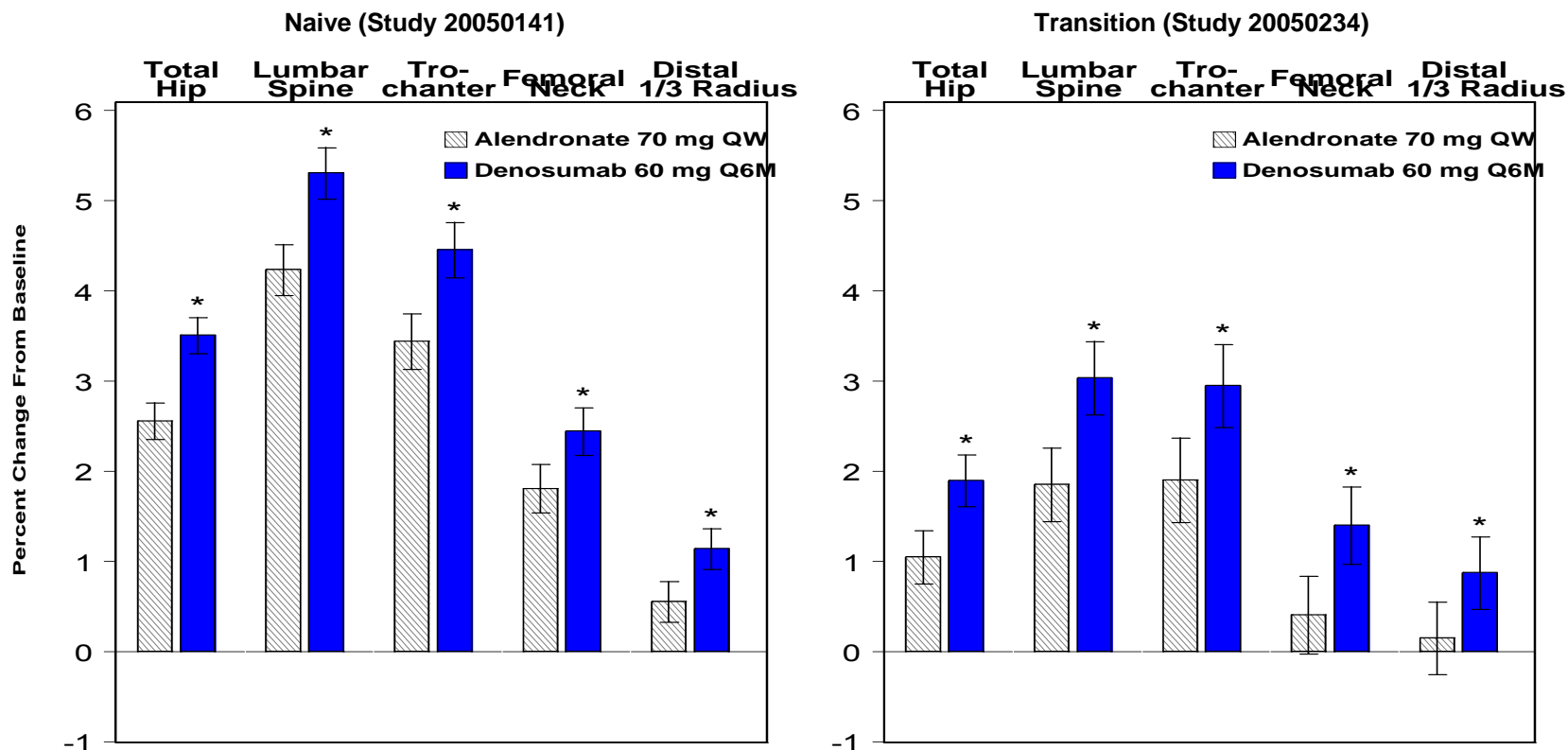


Least squares means with 97.5% CIs for each stratum and 95% CIs for overall assessments based on ANCOVA models (for each stratum) that adjust for treatment, baseline value, machine type, and baseline value-by-machine type interaction; the models (for overall assessment) also adjust for strata

* Indicates significance after multiplicity adjustments at 2.5% level for each stratum and at 5% level for the overall assessment

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Figure 13. Bone Mineral Density by DXA, Percent Change From Baseline in BMD at Month 12 in Head-to-head vs Alendronate Studies (LSM \pm 95% CI; Primary Efficacy Subset)



Number of subjects with values at baseline and at ≥ 1 postbaseline visit:

Study 20050141: alendronate 572 and denosumab 579

Study 20050234: alendronate 241 and denosumab 246

Least squares means with 95% CIs based on an ANCOVA models (for Study 20050141) adjusting for treatment, machine type, baseline value, and baseline value-by-machine type interaction; a repeated measures model (for Study 20050234) adjusting for treatment, length of prior alendronate stratification variable, visit, baseline value, machine type, treatment by visit interaction, and baseline value by machine type interaction

* Indicates significance at a 5% nominal level

Program: /stat/amg162/meta/bla_2008bone/analysis/rhdac/graphs/program/g_dxa_pchg_m12_pmo.sas

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Source Data: a08css.abmdxa

Data from supportive trials suggest that denosumab may improve bone strength, which takes into consideration the bone macroarchitecture and microarchitecture (ie, bone mass and bone quality). A phase 2, randomized, double-blind, double-dummy, placebo-controlled study of postmenopausal women with low BMD (ie, lumbar spine or total hip T-scores from -2.0 to -3.0 [inclusive]) estimated the effect of denosumab compared with placebo and alendronate on BMD and bone geometry parameters assessed by microCT (XtremeCT®) (Study 20050179). XtremeCT® is a novel, precise, high resolution-peripheral quantitative computed tomography (HR-pQCT) technique that allows in-vivo evaluations of bone geometric parameters and compartmental (cortical and trabecular) density in vivo at the distal radius and distal tibia ([Genant et al, 2008](#)). Formal statistical hypothesis testing was not performed for this pilot study.

As assessed by XtremeCT® denosumab increased cortical thickness, BMD of cortical bone, and BMD of trabecular bone at the distal radius compared to placebo ([Table 8](#)). The mean percent increases in these parameters in the denosumab group were of larger magnitudes than those observed in the alendronate group. The increase in cortical thickness is an indication of improved geometry, and the increases in BMD are indications of increased bone mass. Similar results were observed at the distal tibia.

These clinical findings are consistent with nonclinical data in which increases in cortical BMD and thickness were observed with denosumab treatment of adult ovariectomized cynomolgus monkeys that had transitioned from alendronate treatment ($p < 0.05$ vs vehicle-treated controls) ([Ominsky et al, 2009a](#)). These parameters correlated linearly and positively with cortical bone strength. This study also revealed significantly increased trabecular BMD with denosumab, which was accompanied by proportional increases in the strength of trabecular bone samples. The clinical and nonclinical results suggest that denosumab may improve bone strength.

Table 8. Percent Change from Baseline to Month 12 in Cortical and Trabecular BMD and in Cortical Thickness at the Distal Radius Derived by XtremeCT® in Phase 2 Study 20050179 (ANCOVA Model, Efficacy Data Set, LOCF)

	n	% Change From Baseline		Difference From Denosumab 60 mg Q6M	
		LS Mean ^a	95% CI ^a	LS Mean ^a	95% CI ^a
Cortical BMD					
Placebo (N = 79)	79	-1.5	(-1.8, -1.2)	1.8	(1.3,2.2)
Alendronate 70 mg QW (N = 74)	73	-0.3	(-0.6, 0.0)	0.6	(0.1,1.0)
Denosumab 60 mg Q6M (N = 78)	75	0.3	(-0.1, 0.6)		
Trabecular BMD					
Placebo (N = 79)	79	-2.0	(-2.9, -1.0)	2.5	(1.1,3.8)
Alendronate 70 mg QW (N = 74)	73	-0.6	(-1.6, 0.4)	1.1	(-0.3,2.5)
Denosumab 60 mg Q6M (N = 78)	75	0.5	(-0.5, 1.5)		
Cortical Thickness					
Placebo (N = 79)	79	-0.8	(-1.8, 0.3)	4.1	(2.6,5.7)
Alendronate 70 mg QW (N = 74)	73	2.4	(1.2, 3.5)	1.0	(-0.6,2.6)
Denosumab 60 mg Q6M (N = 78)	75	3.4	(2.2, 4.5)		

N = Number of subjects who received ≥ 1 dose of investigational product and have data at baseline and at ≥ 1 postbaseline

LS = Least squares

^a Based on an ANCOVA model adjusting for the baseline value of the variable, age group, and treatment

Source: 20050179 CSR

5.5 Antifracture Efficacy in Women With PMO

Denosumab 60 mg given SC Q6M for 3 years provided robust antifracture efficacy, significantly reducing the risk of new vertebral, nonvertebral, and hip fractures in women with osteoporosis as compared with placebo ([Figure 14](#), [Figure 15](#)). Definitions of fracture categories are provided in [Appendix 2](#).

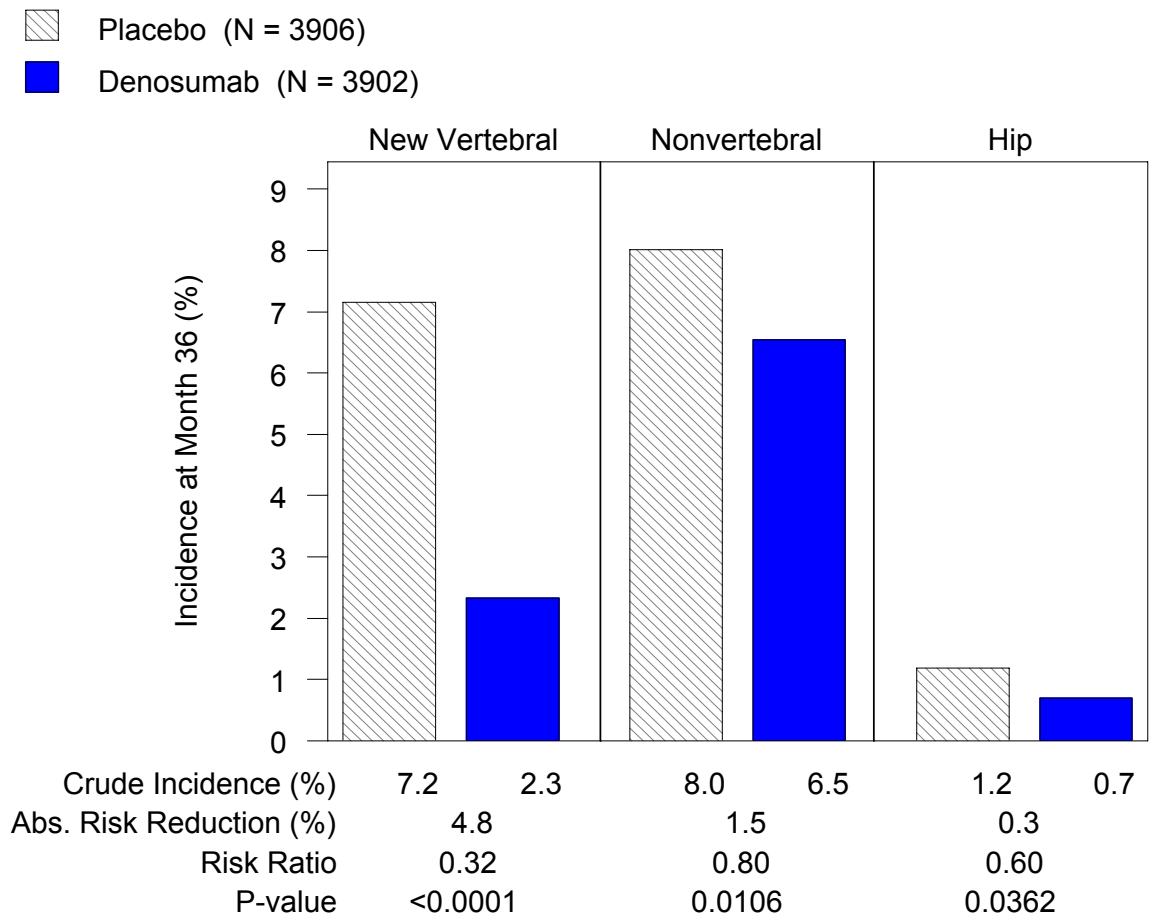
The relative risk reduction at month 36 for new vertebral fractures was 68% ($p < 0.0001$; primary endpoint for the treatment of PMO fracture study [20030216]). The effects of denosumab in preventing new vertebral fractures were rapid and sustained: statistically significant differences between denosumab and placebo groups were observed at 1, 2, and 3 years (post hoc analysis); no attenuation of efficacy over time was observed ([Figure 16](#)). These observations are consistent with the rapid onset of action of denosumab (ie, effect seen at 1 year), and beneficial effects persisted in the subsequent annual intervals.

The reductions in the incidence of new vertebral fracture over 3 years were consistent and significant (based on prespecified subgroup analyses) regardless of baseline age, BMD level, level of bone turnover, prior use of a medication for osteoporosis, and whether or not women had a prevalent vertebral fracture or history of a nonvertebral fracture.

Consistent with the reduction in fracture risk observed for new vertebral fractures, denosumab also reduced the risk of prespecified subcategories of vertebral fractures, ie, new and worsening vertebral fractures, clinical vertebral fractures, and multiple new vertebral fractures (Figure 17). Relative risk reductions at month 36 for nonvertebral and hip fractures were 20% ($p = 0.0106$) and 40% ($p = 0.0362$), respectively (Figure 15).

Nonvertebral fractures occur as a consequence of the sudden application of a force greater than the strength of the bone. The improvement in bone strength required to protect from nonvertebral fractures is greater than that required to protect from vertebral fractures, which generally occur as a result of constant compression. Thus, the nonvertebral fracture end point is difficult to achieve. Denosumab significantly reduced the risk of nonvertebral fractures overall and significantly reduced the risk of combinations of nonvertebral fractures that are more likely associated with osteoporosis: major nonvertebral fractures (relative risk reduction: 20% [$p = 0.0224$]) and major osteoporotic fractures (relative risk reduction: 35% [$p < 0.0001$]) (Figure 17; fracture categories defined in Appendix 2).

Figure 14. Summary of Fracture Efficacy in Treatment of PMO Fracture Study (20030216) (Primary and Secondary Efficacy Endpoints)



Incidence was based on crude incidence for new vertebral fracture and Kaplan-Meier estimate for time to first nonvertebral fracture and hip fracture.

Absolute risk reduction for new vertebral fractures is based on the Mantel-Haenszel method, adjusting for age stratification variable.

Absolute risk reduction for nonvertebral and hip fractures is based on an inverse variance-weighted method, adjusting for age stratification variable.

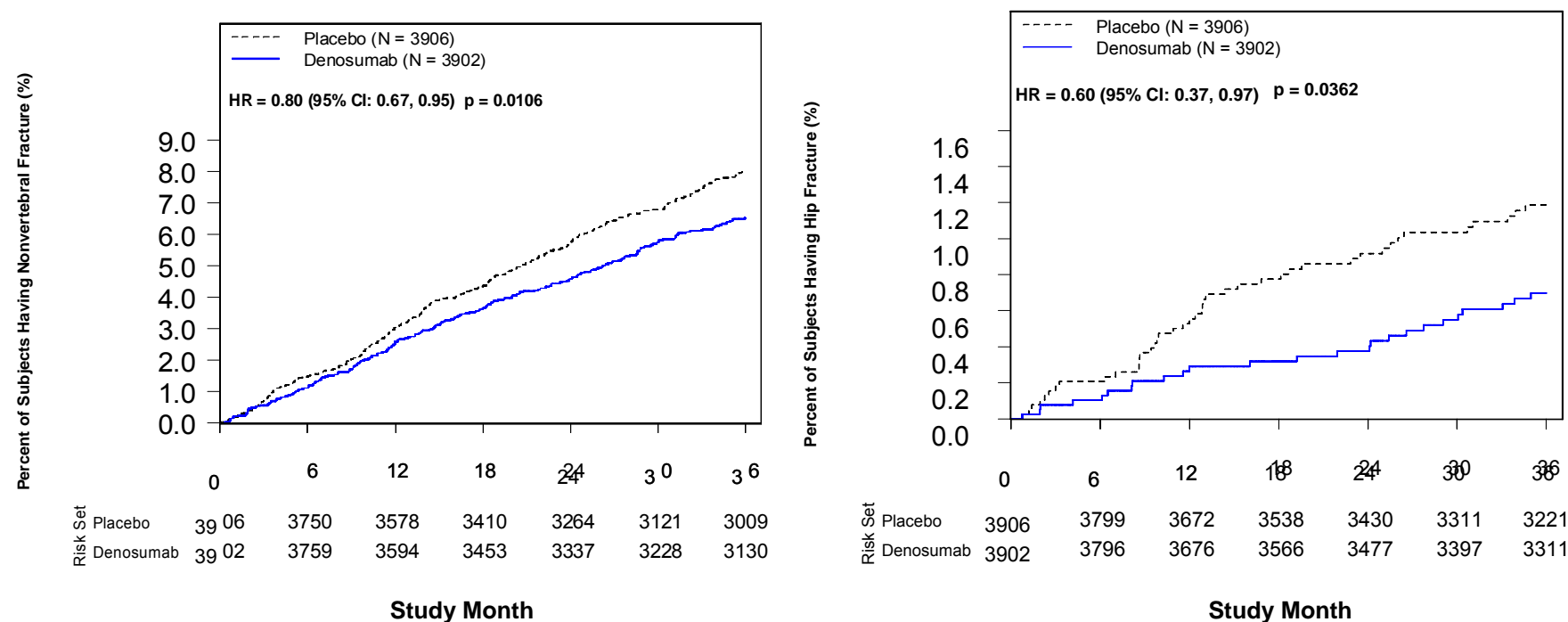
Ratio represents risk ratio for new vertebral fracture and hazard ratio for time to first nonvertebral fracture and hip fracture.

Risk/hazard ratio < 1 favors denosumab.

p-value is based on a logistic regression model adjusting for age stratification variable for new vertebral fracture and a Cox proportional hazards model stratified by age stratification variable for time to first nonvertebral fracture and hip fracture.

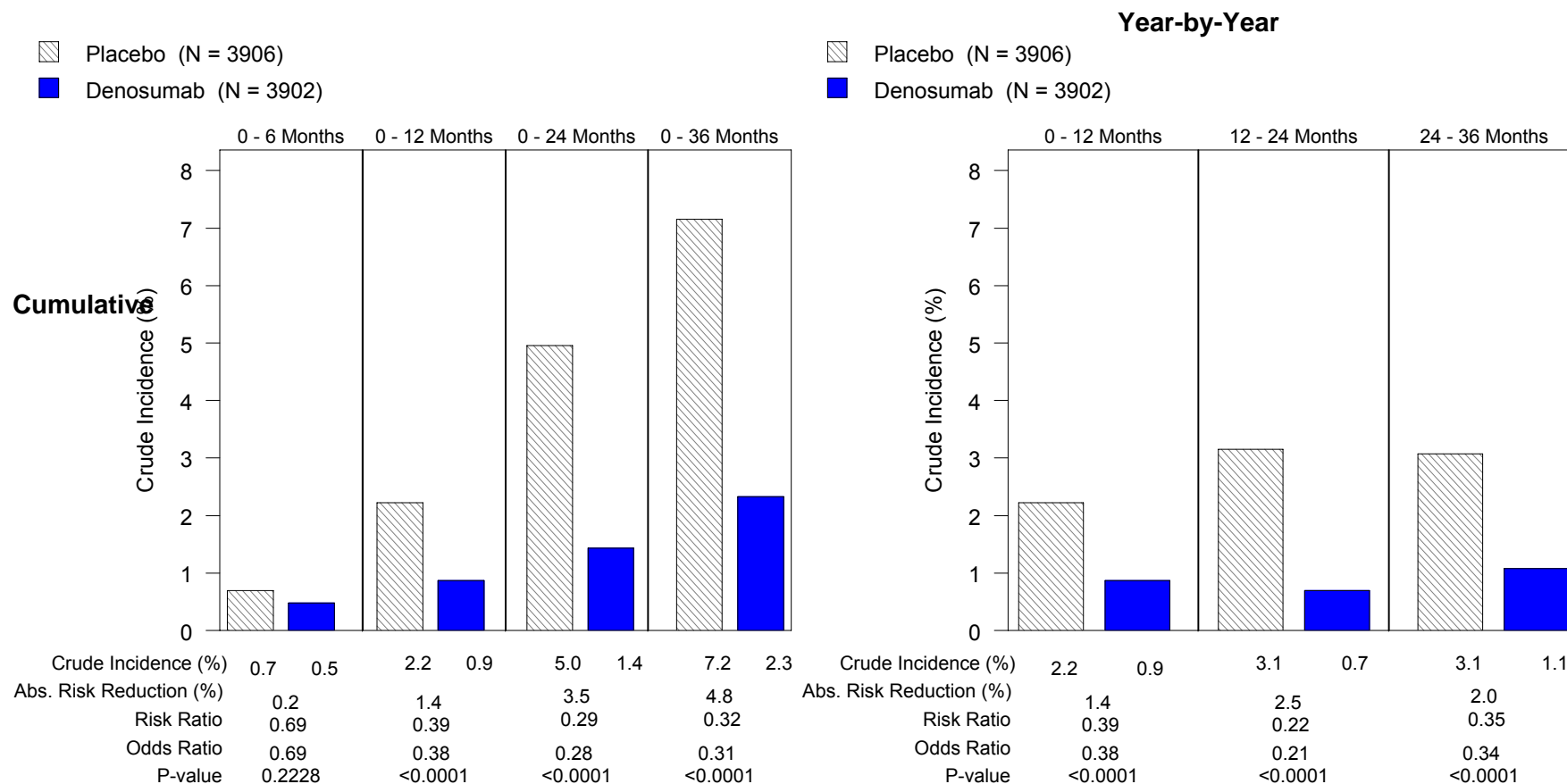
Source: 20030216 CSR

**Figure 15. Time to First Nonvertebral Fracture and Time to First Hip Fracture in Treatment of PMO Fracture Study (20030216)
Kaplan-Meier Curves with 95% CI (Full Analysis Set)**



N = number of subjects randomized.
Source: 20030216 CSR

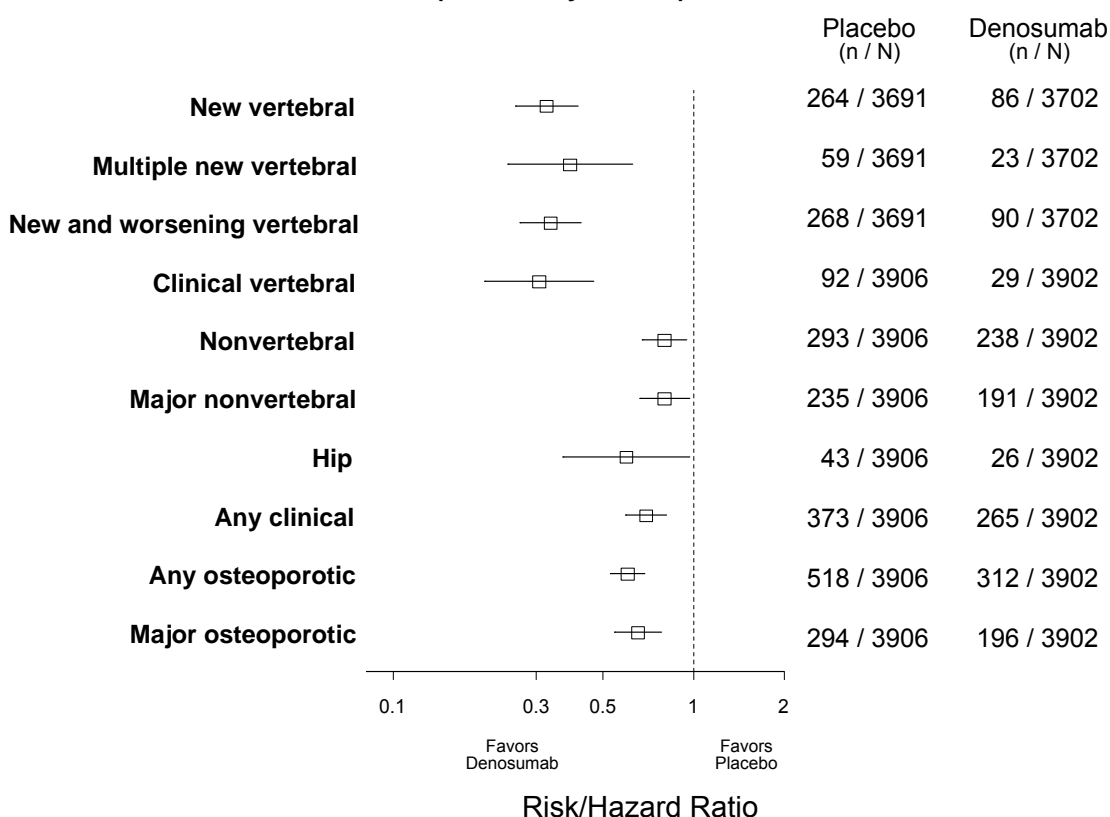
Figure 16. Subject Incidence of New Vertebral Fractures Cumulatively (0-6, 0-12, 0-24, and 0-36 Months) and by Year Separately (Months 0-12, 12-24, 24-36) in Treatment of PMO Fracture Study (20030216) (Primary Efficacy Analysis Set)



“Crude incidence” is the number of subjects with new vertebral fractures during the time period of interest divided by the number of subjects evaluable for new vertebral fractures during the time period of interest. Absolute risk reduction and risk ratio are based on the Mantel-Haenszel method adjusting for age stratification variable. P-values are based on separate logistic regression models adjusting for age stratification variable.

Source: 20030216 CSR

Figure 17. Summary of Antifracture Efficacy Over 3 Years in Treatment of PMO Fracture Study (20030216) (Risk or Hazard Ratio and 95% CI) (Full Analysis Set)



Note: Definitions of fracture categories are provided in [Appendix 2](#).

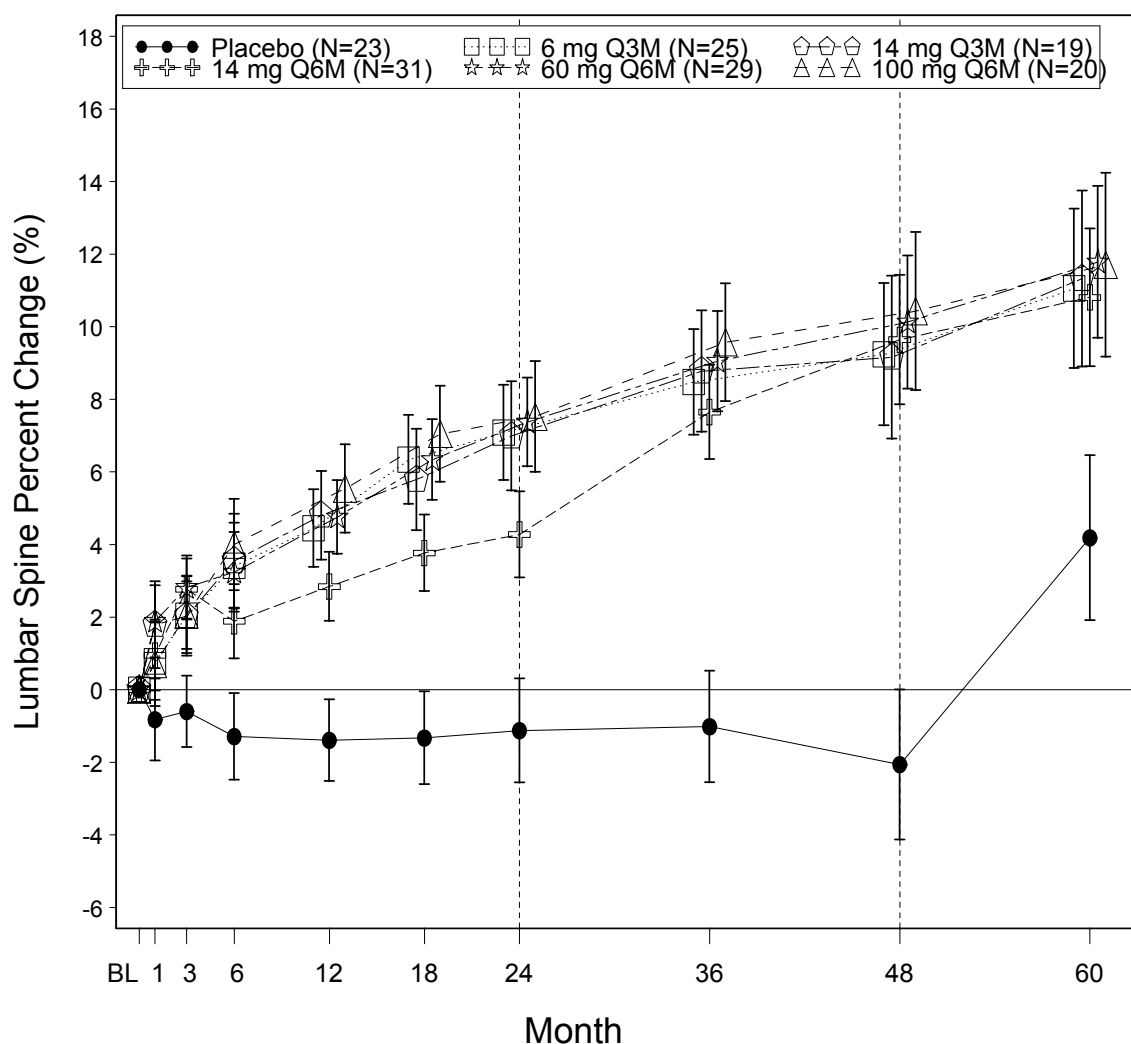
5.6 Long-term Efficacy of Denosumab

In pivotal, 3-year, phase 3 studies in PMO (20030216) and HALT prostate cancer (20040138), the effect of denosumab on fracture efficacy was sustained over the entire 3-year treatment duration. (Efficacy results from the HALT prostate cancer study [20040138] are summarized in [Section 6](#).) The effects of denosumab on antifracture efficacy for new vertebral fractures were rapid and sustained: statistically significant differences between denosumab and placebo groups were observed at 1, 2, and 3 years; no attenuation of efficacy over time was observed (PMO: [Section 5.5](#) ; HALT: [Section 6.5](#)).

BMD data are available for 116 subjects who received denosumab treatment throughout the 4 years of the phase 2 dose-ranging study (20010223) and completed 1 additional year of denosumab treatment during the open-label extension study (20050233). BMD continued to increase over time in subjects who were continuously treated with

denosumab (Figure 18). In addition, reductions in biochemical markers of bone resorption and formation (serum CTX1 and BSAP) were sustained over the course of continuous treatment.

Figure 18. Lumbar Spine BMD Percent Change (LSM \pm 95% CI) From Baseline of Phase 2 Dose-ranging Study (20010223) Through 12 months in the Extension Study (20050233) (Continuous Denosumab Cohorts)



Treatment groups are the original assignments in the phase 2 dose finding study (20010223). Vertical reference lines at 24 and 48 months refer to dose transitions in 20010223 (all subjects in denosumab treatment groups transitioned to the 60 mg Q6M regimen) and beginning of the 20050233 study (placebo group transitioned to denosumab 60 mg Q6M), respectively. Population includes all subjects enrolled in 20050233 with at least 1 baseline (20010223) measurement and at least 1 postbaseline measurement.

Note: Least squares means (LSMs) and 95% confidence intervals (CIs) are from a linear model with percent change from 20010223 baseline value as the dependent variable and treatment, geographic location, and baseline value as independent variables.

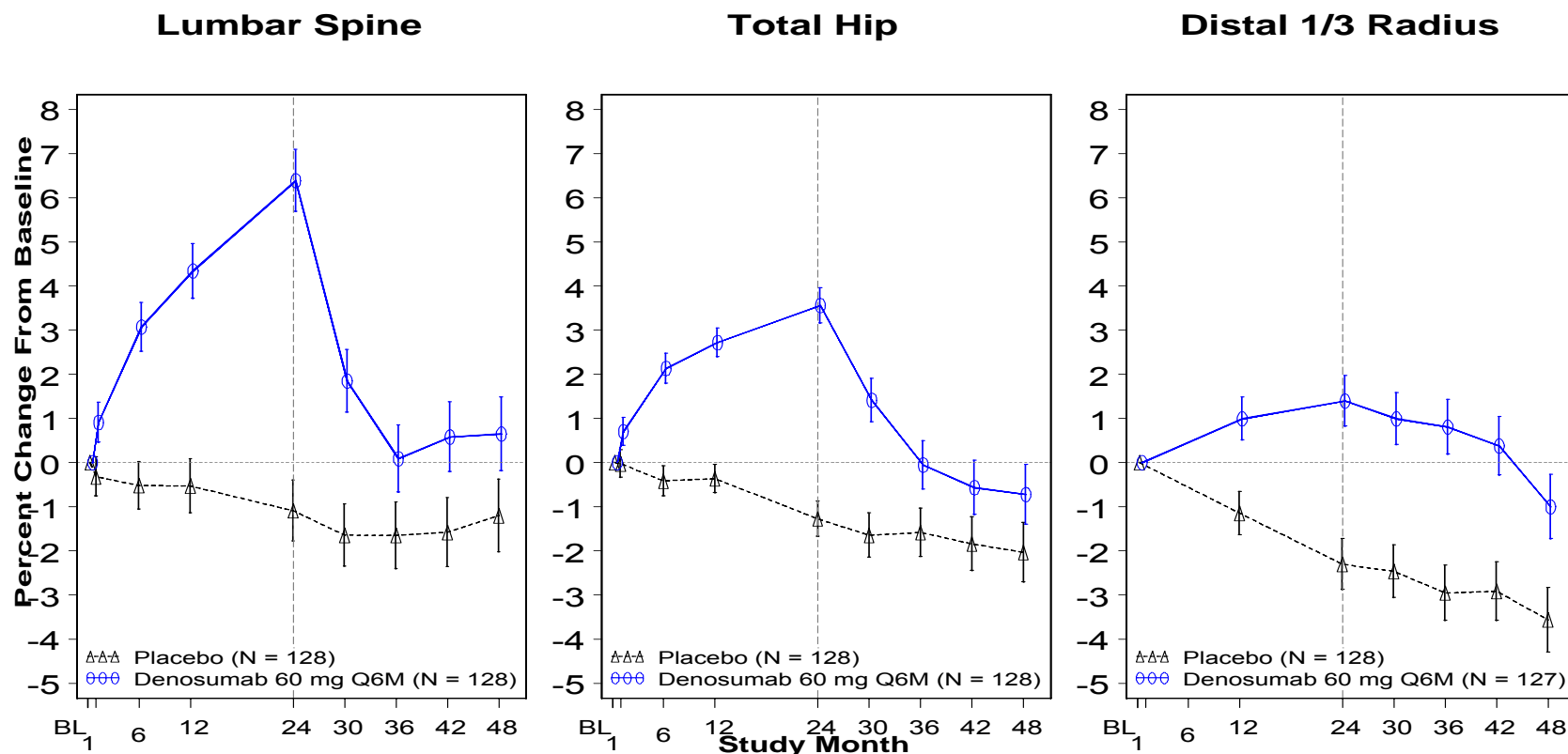
The 7-year extension study (20060289) to the 3-year phase 3 pivotal study (20030216), which includes more than 4500 subjects, will provide additional data regarding long-term efficacy.

5.7 Reversibility of Denosumab Effects in PMO

Denosumab inhibits osteoclast-mediated bone resorption by a targeted mechanism of action ([Section 3.3](#)), which results in improvement in bone strength and prevention of fracture ([Section 5.5](#)) without adverse effects on bone histology ([Section 5.8](#)). Reduction in bone turnover markers with denosumab was rapid and sustained during the entire dosing interval ([Section 5.3](#)). Small attenuation in the degree of reduction in turnover towards the end of the dosing interval correlated closely with the clearance of denosumab from the circulation, demonstrating reversibility of this agent.

The effects of discontinuation of denosumab therapy, as assessed by bone turnover markers and BMD, were evaluated in the phase 2 PMO study (20010223) and the phase 3 prevention of PMO study (20040132). These studies demonstrated that increases in BMD and decreases in bone turnover markers observed with denosumab treatment were reversible ([Figure 19](#) and [Figure 20](#)). BMD generally returned to pretreatment 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 serum CTX1 and P1NP had returned to values near baseline. Bone remodeling remained coupled after treatment was discontinued.

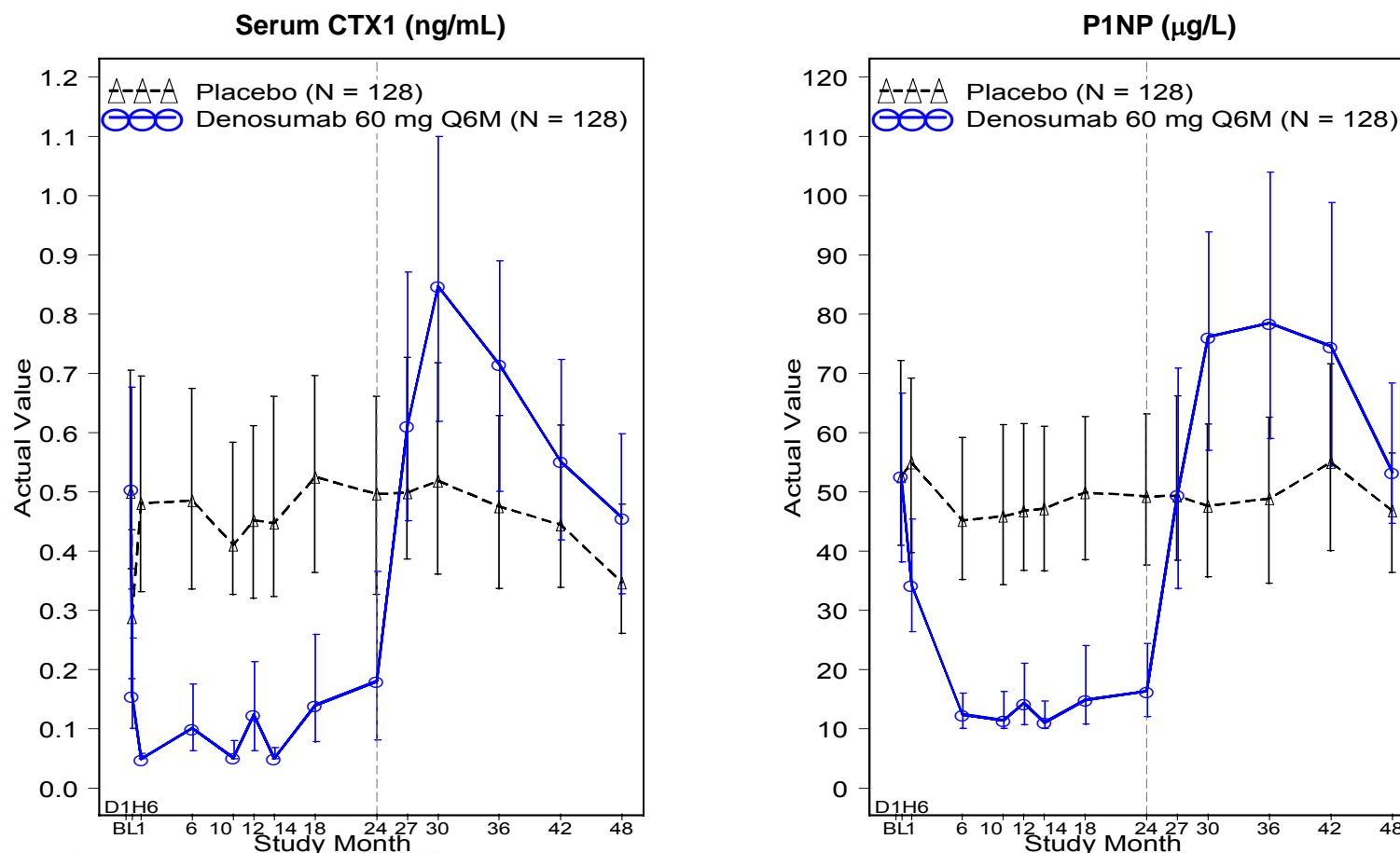
Figure 19. Bone Mineral Density by DXA Percent Change From Baseline by Visit, Least Squares Means and 95% CIs in Prevention of PMO Study (20040132) (Primary Efficacy Subset for Subjects Enrolled in the Off-treatment Phase, No Imputation, Final Analysis [48 Months])



Includes subjects who enrolled in the off-treatment phase with values at baseline and at ≥ 1 postbaseline visit. Least squares means based on repeated measures model that adjusts for treatment, strata, visit, baseline value, machine type, treatment-by-visit interaction, and baseline value-by-machine type interaction. Vertical reference line indicates the end of the double-blind treatment period.

Program: /stat/amg162/meta/bla_2008bone/analysis/rhdac/graphs/program/g_bmd_pchg_visit_rmm_flash.sas
Output: g11-03_009_bmd_pchg_visit_rmm_flash.cgm (Date Generated: 18JUN2009:10:10:14)
Source Data: a132 m48.abmdxa, a132 m48.aslinf

Figure 20. Bone Turnover Markers Serum Concentrations (Median and Interquartile Range) by Visit in Prevention of PMO Study (20040132) (Primary Efficacy Subset for Subjects Enrolled in the Safety Follow-up Phase)



Includes subjects who enrolled in the off-treatment phase
Vertical reference line indicates the end of the double-blind treatment period

Program: /stat/amg162/meta/bla_2008bone/analysis/rhdac/graphs/program/g_btm_act_visit.sas
Output: g1-04_008_001_btm_act_visit.cgm (Date Generated: 18JUN2009:17:45:36)
Source Data: a132 m48.albbnsp, a132 m48.aslinf

The phase 3 prevention of PMO study (20040132) provides additional information on fracture after discontinuation of denosumab treatment (Table 9). In this study, subjects were randomized to treatment with denosumab 60 mg SC Q6M or placebo SC Q6M, for 24 months, after which subject safety was followed up for a further 24 months. BMD, bone turnover markers, and clinical fractures were monitored both during the treatment phase of the study and during the safety follow-up phase. Radiographic evaluation of the spine was performed at 48 months on all subjects and evaluated by a central reader to confirm vertebral fractures. In addition, the central reader evaluated x-rays to confirm fractures in subjects who reported adverse event of fracture. This study was not designed or powered to assess fracture rates in the safety follow-up period.

Table 9. Summary of Fracture Incidence in Safety Follow-up Phase of Prevention of PMO Study (20040132)

Subjects Experiencing Fractures in Safety Follow-up Phase – n(%)	Study 20040132 ^a	
	Placebo (n = 128)	Denosumab (n = 128)
All Fracture Events	5 (3.9%)	9 (7.0%)
Osteoporotic Nonvertebral Fractures	4 (3.1%)	4 (3.1%)
Vertebral Fractures	0 (0%)	2 (1.6%)

^a Complete data for the 2-year off-treatment period
Source: 120-day Safety Update

To further evaluate effects of therapy discontinuation, 2 studies in women with low bone mass or osteoporosis are ongoing to address changes in microstructure by HR-pQCT (20080747) and changes in remodeling at the tissue level by histomorphometry (20080287) after discontinuation of denosumab treatment.

With discontinuation of treatment, BMD and bone turnover markers return to pretreatment levels. Among osteoporosis therapies, postmenopausal estrogen therapy and estrogen receptor agonists/antagonists have reproducibly exhibited this pharmacologic characteristic with therapy discontinuation as assessed by BMD (Greendale et al, 2002; Neele et al, 2002; Tremollieres et al, 2001; Ettinger and Grady, 1993; Felson et al, 1993), bone turnover markers (Thomsen et al, 1987), or both (Wasnich et al, 2004; Ascott-Evans et al, 2003; Sornay-Rendu et al, 2003; Gallagher et al, 2002; Greenspan et al, 2002). Large observational studies with postmenopausal estrogen therapy withdrawal have not shown excess fracture risk after therapy discontinuation (Table 10).

Table 10. Summary of Fracture Incidence in Large Observational Studies After Withdrawal of Postmenopausal Estrogen Therapy

Cohort (Reference)	Time Since Postmenopausal Estrogen Therapy Use	Odds Ratio (95% CI) for Fracture During Discontinuation
Million Women Study (Banks et al, 2004)	< 1 year	1.09 (0.91, 1.3)
	1-2 years	0.96 (0.85, 1.1)
	3-4 years	1.09 (0.93, 1.28)
	≥ 5 years	1.1 (0.97, 1.23)
National Osteoporosis Risk Assessment (NORA) (Barrett-Connor et al, 2003)	≤ 5 years	0.9 (0.71, 1.15)
	6-10 years	0.98 (0.61, 1.57)
	10+ years	1.32 (0.93, 1.87)
NORA hip fracture subset (Yates et al, 2004)	≤ 5 years	1.65 (1.05, 2.59)
Women's Health Initiative (WHI) (Heiss et al, 2008)	3 years	Hip: 0.92 (0.64, 1.34)
		Vertebral: 0.96 (0.64, 1.44)
		Other: 0.87 (0.74, 1.03)
		All fractures: 0.91 (0.78, 1.06)

Reversibility, as measured by BMD and bone turnover markers, has also been observed with the anabolic agent, teriparatide ([Lindsay et al, 2004](#), [Prince et al, 2005](#)). Evidence of reversibility within the bisphosphonate class varies by compound affinity to hydroxyapatite: etidronate, risedronate, and ibandronate have lower affinity, and alendronate and zoledronic acid have higher affinity ([Miller, 2008](#)). Clinical consequences of adsorption affinity are reflected with discontinuation of treatment. Prompt increases in bone turnover and declines in BMD have been observed 12 months after discontinuation of risedronate ([Watts et al, 2008](#)), compared with gradual changes over a few years after discontinuation of alendronate ([Black et al, 2006](#)).

Sustained benefit of a therapeutic for a chronic condition generally requires continued treatment. Effects of pharmacologic agents often are not sustained once treatment is discontinued, as has been observed in management of many disease states, including hypertension or diabetes mellitus. Denosumab, a potential therapy for osteoporosis, is a soluble inhibitor of RANKL and, therefore, does not incorporate into bone matrix. Discontinuation of denosumab resulted in increases in bone turnover and declines in

BMD that are similar to those therapies that do not have binding affinity for hydroxyapatite in matrix, including hormone therapy.

5.8 Bone Histology and Histomorphometry

The effects of denosumab on bone were also assessed through histology, which evaluated indices of bone quality, and through histomorphometry, which assessed variables of bone remodeling, in clinical and nonclinical studies. Bone biopsies were obtained from the transiliac crest. Before the biopsy procedure, a standard double-label tetracycline procedure was conducted that allowed for calculation of rate-dependent bone remodeling variables.

Bone biopsies were obtained at:

- months 24 and 36 in a subset of subjects who received denosumab or placebo in the treatment of PMO fracture study (20030216)
- month 12 in a subset of subjects who were pretreated with alendronate and either continued alendronate therapy or transitioned to denosumab in the head-to-head vs alendronate (transition) study (20050234)
- baseline and month 12 in a subset of subjects who were treated with denosumab, alendronate, or placebo in the phase 2 dose-ranging study (20010223)

In these studies, bone biopsy results in subjects treated with denosumab for up to 36 months revealed normal bone architecture, lamellar appearance, and mineralization, and an absence of pathology, including marrow fibrosis, osteomalacia, or woven bone. These findings showed that bone was of normal quality.

Consistent with the denosumab mechanism of action and the observed reduction in bone turnover markers, histomorphometric findings demonstrated significant decreases in bone turnover parameters in denosumab-treated subjects ([Table 11](#)). The magnitude of bone turnover reduction resulted in a decrease in tetracycline uptake by the bone. As a consequence, there were fewer biopsy specimens showing fluorescent tetracycline labels in patients treated with denosumab ([Table 12](#)). Fluorescent tetracycline label is required for the calculation of histomorphometric parameters; therefore, a limited number of samples in the denosumab group were available to measure and calculate parameters of bone turnover.

Table 11. Bone Histomorphometric Parameters at Month 24 and 36 Combined Treatment of PMO Fracture Study (20030216) (Bone Biopsy Substudy Analysis Set)

	Placebo (N1 = 45)		Denosumab 60 mg Q6M (N1 = 47)		p-value ^a
	n	Median (Q1,Q3)	n	Median (Q1,Q3)	
Mineral apposition rate ($\mu\text{m}/\text{day}$)	37	0.750 (0.660, 0.830)	7	0.300 (0.300, 0.500)	0.0003
Bone formation rate - surface based ($\mu\text{m}^3/\mu\text{m}^2/\text{year}$)	37	9.210 (5.250, 17.480)	7	0.220 (0.130, 0.350)	<.0001
Activation frequency (/year)	37	0.200 (0.120, 0.330)	7	0.002 (0.001, 0.004)	<.0001

Note: Only includes the month-36 data if subject has data from both time points

n = Number of subjects with observed data

N1 = Number of subjects who enrolled in the bone biopsy substudy, received ≥ 1 dose of investigational product, and had ≥ 1 evaluable biopsy

^a Based on the Wilcoxon rank sum test

Source: 20030216 CSR

Table 12. Labeling Status in Trabecular or Cortical Compartments in Treatment of PMO Fracture Study (20030216) (Bone Biopsy Substudy Analysis Set)

	Placebo n (%)	Denosumab 60 mg Q6M n (%)
Number of evaluable biopsies obtained at month 24 or 36	62	53
Any label	62 (100)	34 (64)
Any double label	62 (100)	21 (40)
Only single label	0 (0)	13 (25)
No label	0 (0)	19 (36)

n = Number of biopsies

Percentages based on the number of evaluable biopsies at the time points of interest

Any double label includes only double label or both single and double label observed for trabecular or cortical compartment.

Only single label includes biopsies where single label was observed for both trabecular and cortical compartments or only single label was observed for one of trabecular or cortical compartments and no label for the other.

No label includes biopsies where no label was observed in either trabecular or cortical compartment.

Source: 20030216 CSR

Amgen also conducted a long-term bone quality study of ovariectomized (OVX) adult (9- to 16-year-old) cynomolgus monkeys. Monkeys were treated with 25 to 50 mg/kg of

denosumab or placebo QM and histomorphometry and biomechanical strength testing were evaluated. Denosumab administration was associated with significant reductions in bone remodeling as assessed by both bone turnover markers and histomorphometry. Nearly all primates (29 of 31) showed no evidence of double fluorochrome-labeled surfaces, suggesting that bone turnover was significantly reduced. Vertebral trabecular peak load, a measurement of biomechanical strength, in 28 of the 29 samples with no double label exceeded the average peak load value of the vehicle-treated OVX control samples. These findings indicate that, although denosumab significantly decreased bone turnover, as evidenced by reductions in bone turnover markers and very low levels of remodeling at the tissue level, these reductions in bone turnover were associated with, and proportional to, increases in bone strength.

Denosumab inhibits bone resorption by a targeted mechanism of action, which results in improvements in bone strength and prevention of fracture without adverse effects on bone histology.

6. Clinical Efficacy of Denosumab for the Treatment of Bone Loss Due to HALT

6.1 Key Points

- The clinical development program in bone loss due to HALT is supported by the following key studies:
 - Pivotal, phase 3, HALT prostate cancer study (20040138) (n = 1468)
 - Pivotal, phase 3, HALT breast cancer study (20040135) (n = 252)
- Denosumab significantly increased BMD at all skeletal sites in both women and men with bone loss due to HALT. Increases were consistent with those observed in women with PMO.
- Denosumab reduced the risk of new vertebral fracture by 62% in men with prostate cancer receiving androgen deprivation therapy (ADT). Effects were observed at 1 year and were sustained for 3 years. Reductions in vertebral fracture risk were consistent with those observed in women with PMO.

6.2 Demographics and Disposition in HALT Studies

Demographics of subjects in these studies reflected the cancers treated with HALT. All subjects in the prostate cancer study (20040138) were men, and all subjects in the breast cancer study (20040135) were women. Subjects in the prostate cancer study were older than subjects in the breast cancer study (mean ages: 75.4 vs 59.5 years), and a greater proportion of subjects in the prostate cancer study were ≥ 65 years of age (93% vs 30%). Consistent with the eligibility criteria ([Table 2](#)), mean BMD T-scores at the lumbar spine were higher in the prostate cancer study (-0.36 vs -1.06). In the prostate and breast cancer studies, 22% and 6% of subjects, respectively, had at least 1 prevalent vertebral fracture at baseline.

Table 13. Summary of Demographics Disposition of Key PMO Studies

	HALT Prostate Cancer (20040138)	HALT Breast Cancer (20040135)
n	1468	252
% Women	0%	100%
% White	83%	93%
Mean (SD) age (years)	75.4 (7.1)	59.5 (9.3)
Mean (SD) BMD T-score at the lumbar spine	-0.36 (1.79)	-1.06 (0.90)
Mean (SD) years since last menstrual period	-	12.9 (10.5)
% Prevalent vertebral fractures at baseline ^a	22%	6%
% Completed Study ^b	62%	81%

^a Based on radiographic assessments for Study 20040138 and on medical history for Study 20040135.

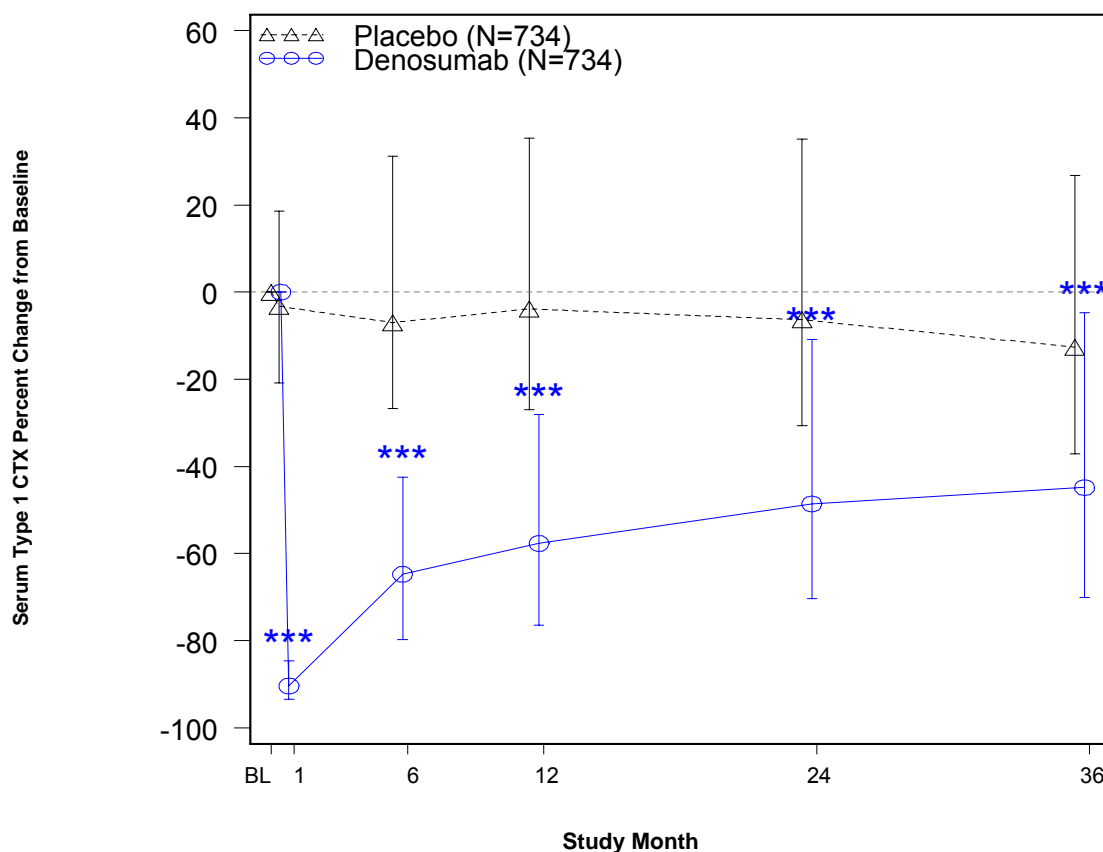
^b Completion of the 3-year (20040138) or 2-year (20040135) treatment period

Source: 20040138 and 20040135 CSRs

6.3 Denosumab Effects on Bone Turnover Markers

In both Studies 20040135 and 20040138, denosumab administration resulted in marked, rapid, and sustained decreases in serum concentrations of CTX1 ([Figure 21](#)), P1NP, and TRAP 5b (TRAP 5b evaluated in Study 20040138 only) relative to placebo ($p < 0.0001$ at all time points). The antiresorptive effect of denosumab was evident at month 1 (the earliest assessment time point) with median decreases in serum CTX1 of 90% and 91% in prostate cancer (20040138) and breast cancer (20040135) studies, respectively. Although serum CTX1 remained statistically significantly reduced prior to the next dose, a small attenuation of effect was observed over the dosing interval, reflecting the reversibility of denosumab's effects on bone as serum drug levels diminish. This dynamic profile is a characteristic of denosumab and is also observed in the PMO setting ([Section 5.3](#)). As in the PMO setting, decreases in bone resorption markers were followed by reductions in bone formation markers in both HALT studies.

Figure 21. Median Percent Change (Interquartile Range) From Baseline in Serum CTX1 in HALT Prostate Cancer Study (20040138) (Observed Data Analysis Set)



N = Number of subjects randomized

CTX = C-Telopeptide

P-values based on the van Elteren rank test stratified by age group and ADT duration at study entry

* statistically significant (p-value ≤ 0.05); ** statistically significant (p-value ≤ 0.025);

*** statistically significant (p-value ≤ 0.01)

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Source Data: adam.albbnsp, adam.aslinfo

6.4 Denosumab Effects on BMD

Denosumab was consistently efficacious in increasing BMD across the spectrum of subjects evaluated in denosumab clinical studies, regardless of type and duration of HALT (AIT in Study 20040135 and ADT in Study 20040138) (Figure 22). Across both studies, increases in BMD were observed as early as 1 month after the initial dose and were sustained throughout the treatment period (24 months in Study 20040135 and 36 months in Study 20040138). Statistically significant increases of BMD were observed in both predominantly trabecular and predominantly cortical bone sites (Figure 23).

Increases in BMD were demonstrated by the primary endpoints of the HALT studies. In the HALT prostate cancer study (20040138), the mean change in lumbar spine BMD at

month 24 (the primary endpoint) was 5.6% in the denosumab group compared with -1.0% in the placebo group, a statistically and clinically significant difference of 6.7% (95% CI: 6.2, 7.1) ($p < 0.0001$). In the HALT breast cancer study (20040135), the mean change in lumbar spine BMD at month 12 (the primary endpoint) was 4.8% in the denosumab group compared with -0.7% in the placebo group, a statistically and clinically significant difference of 5.5% (95% CI: 4.8, 6.3) ($p < 0.0001$).

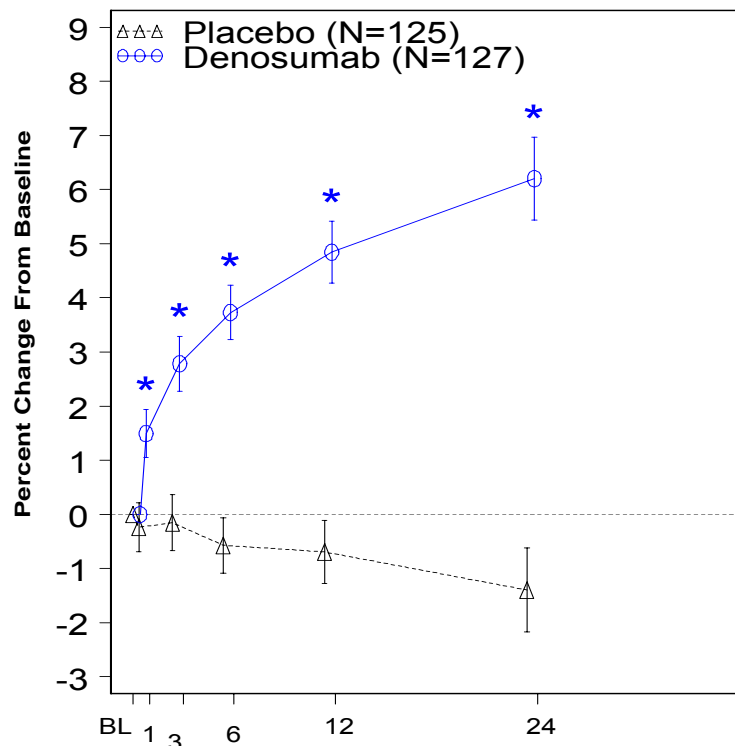
Efficacy in increasing BMD also was demonstrated at the end of the treatment periods of the HALT studies. In the HALT prostate cancer study (20040138), denosumab increased lumbar spine BMD by 7.9%, total hip BMD by 5.7%, femoral neck BMD by 4.9%, hip trochanter BMD by 6.9%, distal 1/3 radius BMD by 6.9%, and total body BMD by 4.7% over 3 years, relative to placebo (all $p < 0.0001$). In the HALT breast cancer study (20040135), denosumab increased lumbar spine BMD by 7.6%, total hip BMD by 4.7%, femoral neck BMD by 3.6%, hip trochanter BMD by 5.9%, distal 1/3 radius BMD by 6.1%, and total body BMD by 4.2% over 2 years, relative to placebo (all $p < 0.0001$).

In both studies, increases in BMD were demonstrated in the denosumab group compared with the placebo group at all skeletal sites assessed. The increases in BMD at the distal 1/3 radius are particularly noteworthy given the large decrease in BMD at this site in the placebo group ([Figure 23](#)).

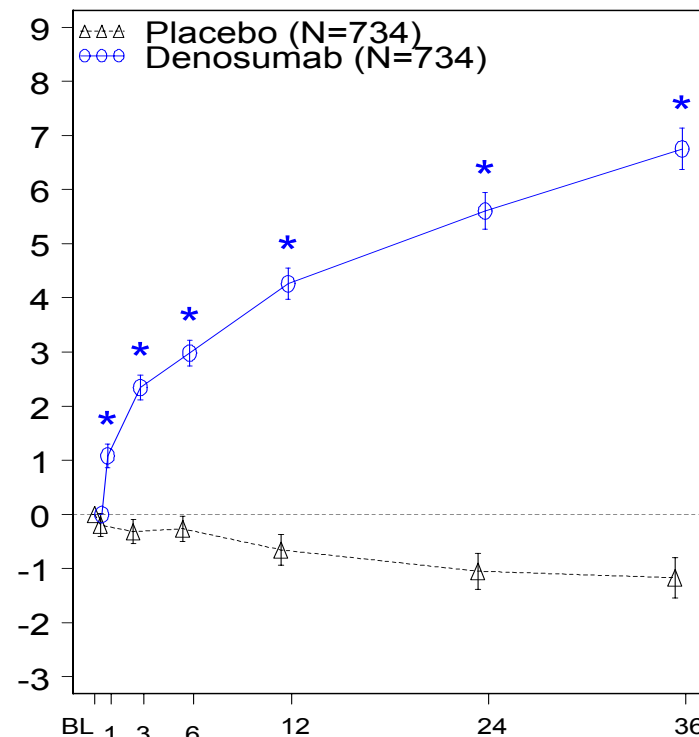
Denosumab increased BMD across subgroups of baseline characteristics. In the HALT prostate cancer study (20040138), denosumab significantly increased BMD from baseline to month 36 in all subgroups examined (age, weight, BMI, duration of hormone-ablative therapy, race, baseline lumbar spine BMD T-score, serum CTX1, prevalent vertebral fracture, and geographic region). Similarly, in the HALT breast cancer study (20040135), denosumab significantly increased BMD from baseline to month 24 in all subgroups examined (age, weight, BMI, duration of hormone-ablative therapy, prior chemotherapy, prior administration of estrogen receptor agonists/antagonists, and time from last menstrual cycle). The magnitude of the treatment effect was similar across the subgroups analyzed within each study.

**Figure 22. Percent Change From Baseline in Lumbar Spine BMD in HALT Studies (Assessed by DXA)
(Least Squares Means and 95% CIs From ANCOVA Model) (Primary Efficacy Subset, LOCF)**

Phase 3 HALT Breast Cancer (Study 20040135, 24 months)



Phase 3 HALT Prostate Cancer (Study 20040138, 36-months)



Study Month

N = Number of subjects randomized

Point estimates and nominal 95% confidence intervals based on an ANCOVA model adjusting for treatment, stratification factor(s), baseline value, machine type, and baseline value-by-machine type interaction.

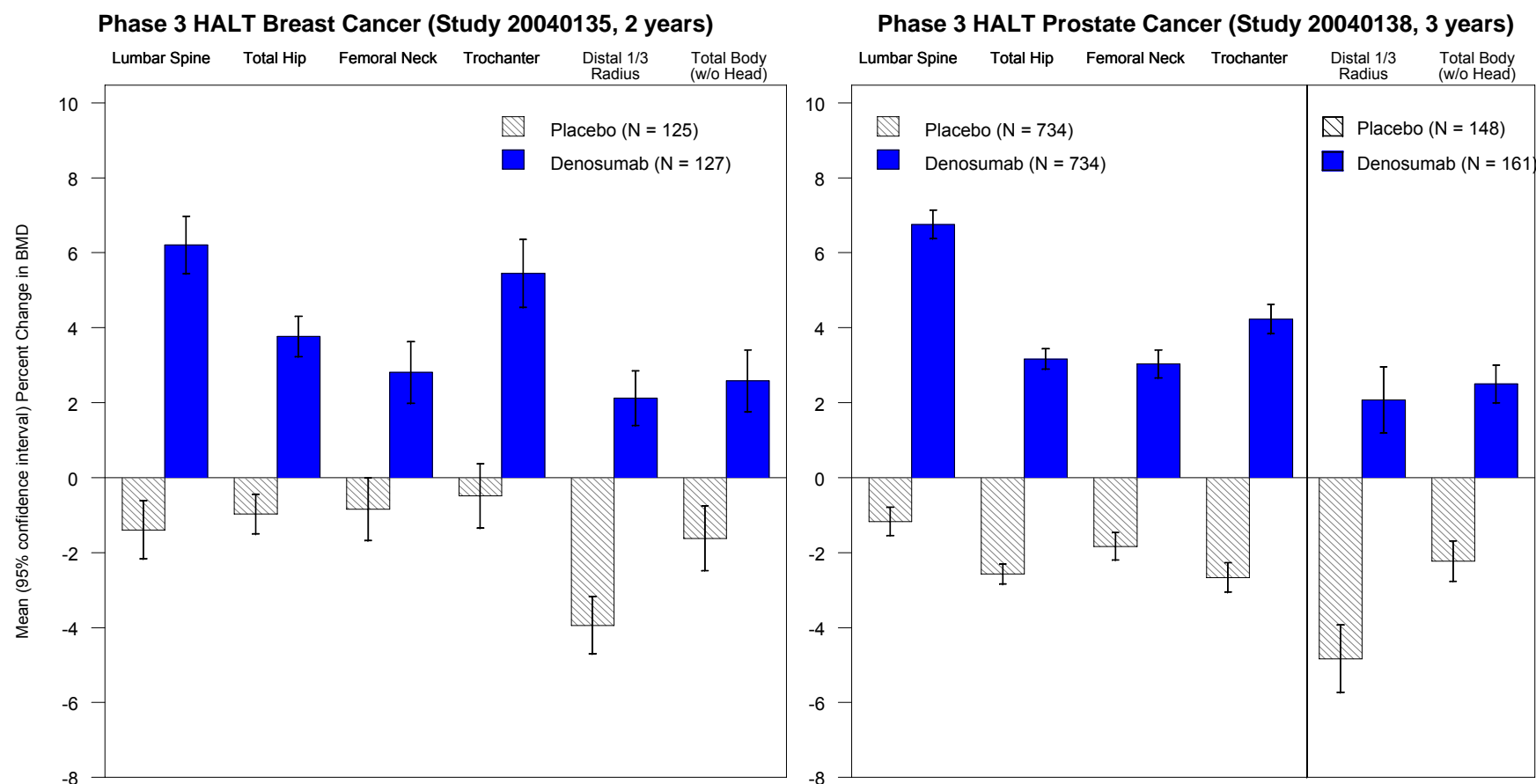
* statistically significant (p-value ≤ 0.05)

Program: /stat/amg162/meta/bla_2008bone/analysis/cse/graphs/program/g_dxa_pchg_halt.sas

Output: ge2-04_001_001_dxa_pchg_locf_1spn_halt.cgm (Date Generated: 17SEP2008: 8:39:25)

Source Data: adam.abmdxa, adam.aslinf

Figure 23. Bone Mineral Density by DXA, Percent Change From Baseline to End of Study, in HALT Studies
Least Squares Means and CIs From ANCOVA Model (LOCF Imputation)



N = Number of subjects randomized. Point estimates and nominal 95% confidence intervals are based on an ANCOVA models adjusting for baseline value, machine type, and baseline value-by-machine type interaction (both studies); for stratification variable (20040135); and for age group and ADT duration at study entry (20040135).

6.5 Antifracture Efficacy in Men With Prostate Cancer Receiving ADT

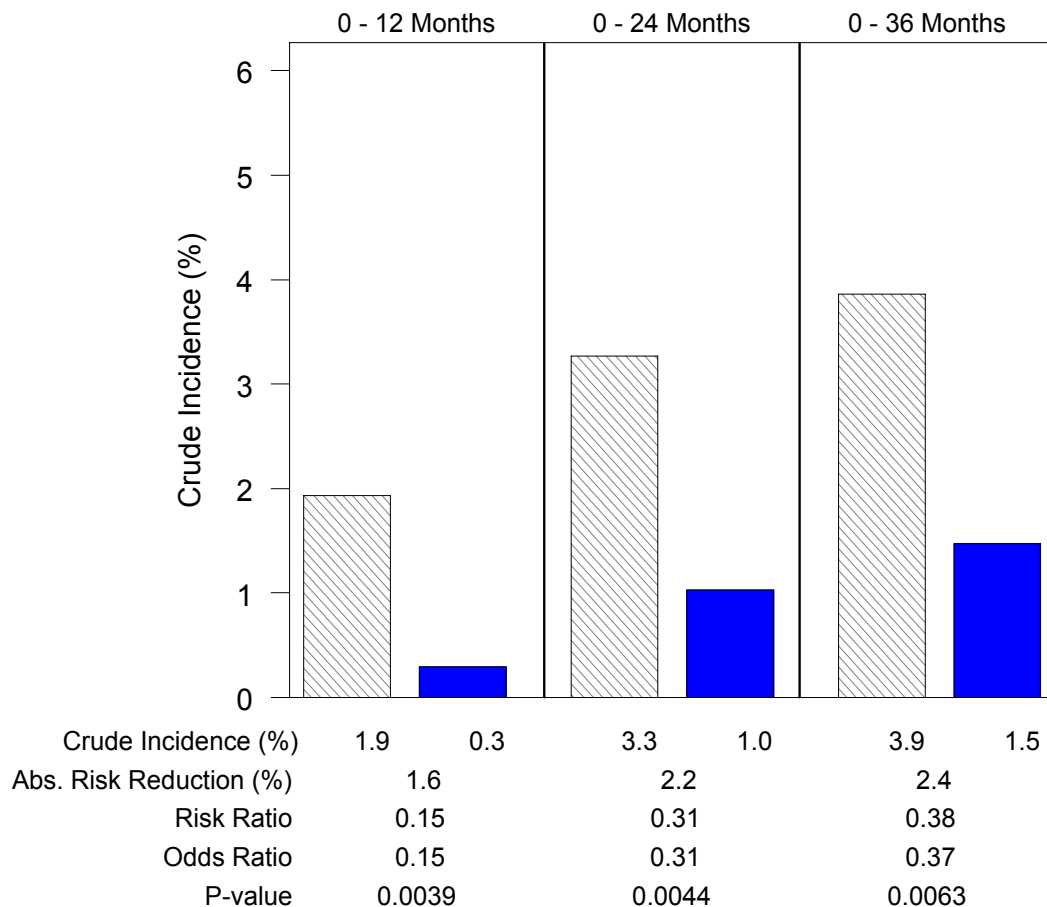
The HALT prostate cancer study (20040138) included prespecified secondary and exploratory endpoints for fracture ([Table 3](#)). In this study, denosumab significantly reduced the risk of new vertebral fractures relative to placebo through month 36 by 62% (relative risk, 0.38; 95% CI, 0.19 to 0.78; unadjusted $p = 0.0063$, adjusted for multiplicity $p = 0.0125$) ([Figure 24](#) and [Table 14](#)). The incidence of new vertebral fractures through month 36 was 1.5% in the denosumab group and 3.9% in the placebo group. This difference was apparent in the first year and was also observed in the second and third years. Definitions of fracture categories are provided in [Appendix 2](#).

Consistent with the results for new vertebral fracture, denosumab also reduced the incidence of new and worsening vertebral fractures through month 36 by 58% ($p = 0.0114$). In addition, there was a reduction in the risk of any osteoporotic fracture in the denosumab group compared with the placebo group at month 36, although the difference between groups was not statistically significant ($p = 0.1048$) ([Table 14](#)). In a prespecified exploratory analysis, denosumab also reduced the risk of multiple fractures at any site by 72% ($p = 0.0063$) relative to placebo over 36 months. Results of other fracture secondary endpoints, including time to first clinical fracture, were not significantly different between the denosumab and placebo groups.

Overall, the treatment effect of denosumab on vertebral fractures observed in men with nonmetastatic prostate cancer undergoing ADT was similar to that observed in the studies of PMO ([Section 6.6](#)). These results demonstrate the antifracture efficacy of denosumab in this patient population and that denosumab has the potential to address a significant unmet medical need ([Guise, 2006](#); [Shahinian et al, 2005](#)).

**Figure 24. Subject Incidence of New Vertebral Fractures in the Phase 3 HALT Prostate Cancer Study (20040138)
(Cumulative: 0-12, 0-24, and 0-36 Months) (Vertebral Fracture Analysis Set)**

▨ Placebo (N = 673)
■ Denosumab (N = 679)



Absolute risk reduction and risk ratio are based on the Mantel-Haenszel method, adjusting for stratification variable. P-values are based on separate logistic regression models adjusting for stratification variable.

Risk ratio < 1 favors denosumab.

Source: 20040138 CSR

Table 14. Summary of Fracture Secondary Endpoints in the Phase 3 HALT Prostate Cancer Study (20040138)

Fracture Endpoint	Denosumab Placebo 60 mg Q6M (N=734) (N=734)		Estimate	95% CI	p-value	Adjusted p-value ^a
	n	n				
Subject Incidence of Any Fracture Through Month 36 ^b	734	734	0.70 ^b	(0.46, 1.08)	0.1048	0.1048
Subject Incidence of New Vertebral Fracture Through Month 36 ^{b,d}	673	679	0.37 ^b	(0.18, 0.78)	0.0063	0.0125
Time to First Clinical Fracture Through Month 36 ^c	734	734	0.94 ^c	(0.57, 1.55)	0.7961	0.7961
Subject Incidence of Any Fracture Through Month 24 ^b	734	734	0.70 ^b	(0.44, 1.11)	0.1282	0.7961

N = Number of subjects randomized.

^a P-values for all endpoints adjusted for multiplicity according to the prespecified sequential testing strategy.

^b Odds ratio relative to placebo based on logistic regression model adjusting for the stratification variables of age group and ADT duration at study entry.

^c Hazard ratio relative to placebo based on Cox proportional hazards model stratified by the stratification variables of age group and ADT duration at study entry.

^d Only subjects with a nonmissing baseline and ≥ 1 postbaseline assessment were included.

Source: 20040138 CSR

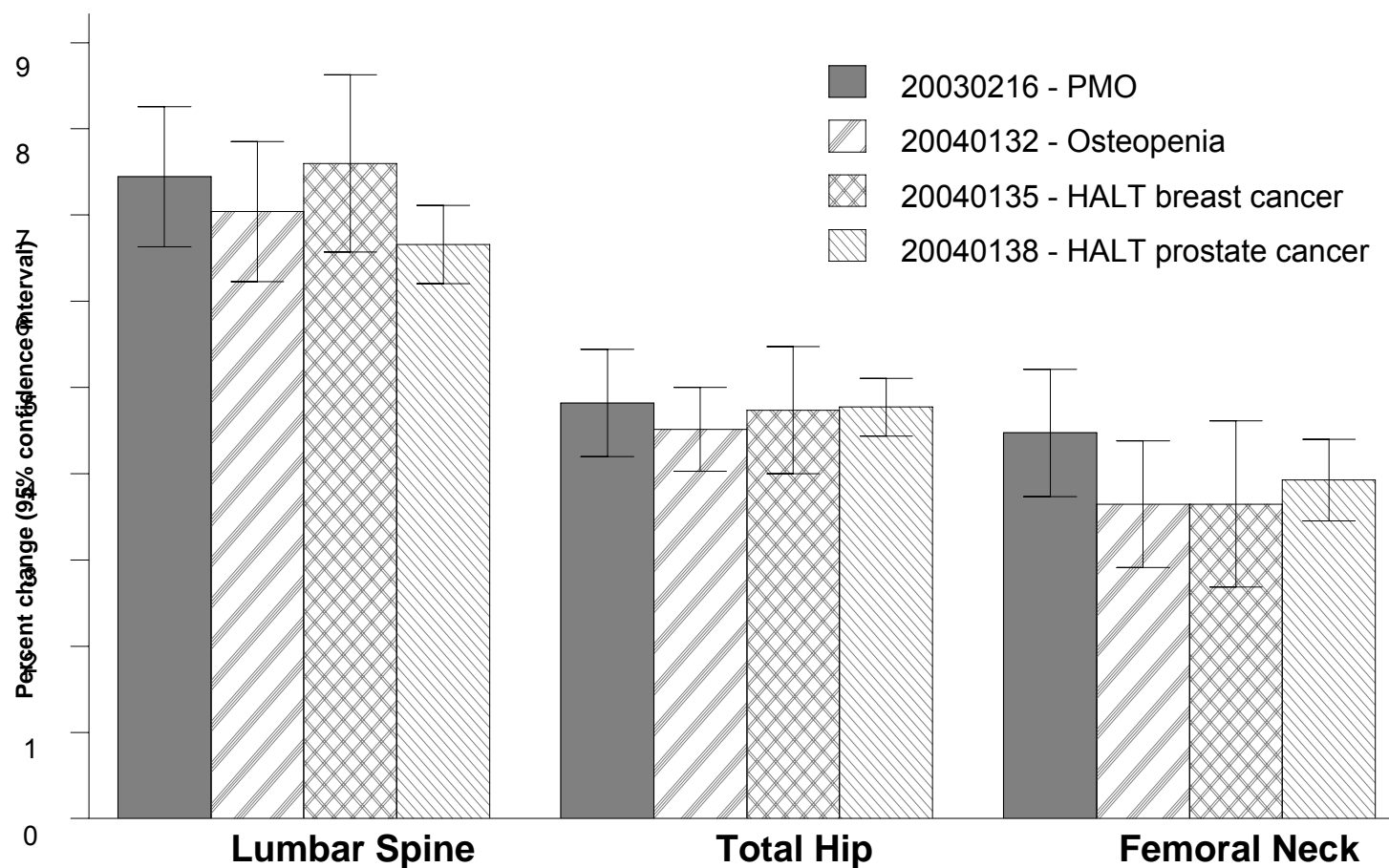
6.6 Consistency in Efficacy Between PMO and HALT Settings

The magnitude of the treatment effect for new vertebral fracture in the phase 3 HALT prostate cancer study (20040138) (62% reduction; [Figure 24](#)) was similar to that observed in women with PMO in the phase 3 fracture study (20030216) (68% reduction, [Figure 14](#)).

The magnitudes of the increases in BMD at 2 years in the phase 3 HALT studies also were similar to those observed in the treatment of PMO fracture study (20030216) and the prevention of PMO study (20040132) ([Figure 25](#)). BMD increases at 3 years (difference between denosumab and placebo groups in change from baseline) were similar in the treatment of PMO fracture and HALT prostate cancer studies for lumbar spine (8.8% PMO, 7.9% HALT), total hip (6.4%, 5.7%), and femoral neck (5.2%, 4.9%).

The HALT breast cancer study (20040135) was not designed or powered to evaluate fracture efficacy; however, based on the consistency of denosumab's effect on BMD in all clinical settings explored to date, it is reasonable to extrapolate that denosumab, 60 mg SC Q6M, will have antifracture efficacy in women with nonmetastatic breast cancer receiving AIT.

Figure 25. Difference Between Denosumab and Placebo Treatment Groups in Mean Percent Change in BMD From Baseline to Month 24 in Phase 3 Pivotal Studies (ANCOVA, LOCF)



20030216: Data presented from DXA substudy

Program: /stat/amg162/meta/bla_2008bone/analysis/rhdac/graphs/program/g_bar_bmd_lsm_pchg.sas
Output: g1-04_002_001_bar_bmd_lsm_pchg.cgm (Date Generated: 17JUN2009: 9:02:13)
Source Data: a08css.abmdxa

6.7 Off-treatment Follow-up in HALT Studies

The phase 3 HALT prostate cancer (20040138) and breast cancer (20040135) studies provide information on fracture after discontinuation of denosumab treatment (Table 15). In both studies, subjects were randomized to treatment with denosumab 60 mg SC Q6M or placebo SC Q6M, for either 24 months (Study 20040135) or 36 months (Study 20040138), after which subject safety was, or will be, followed up for a further 24 months. No scheduled imaging or radiographic confirmation of fractures was performed in these studies, and these studies were not designed or powered to assess fracture rates in the safety follow-up periods.

Table 15. Summary of Fracture Incidence in Safety Follow-up Phases of HALT Prostate Cancer Study (20040138) and HALT Breast Cancer Study (20040135)

Subjects Experiencing Fractures in Safety Follow-up Phase – n(%)	Study 20040138 ^a		Study 20040135 ^a	
	Placebo (n = 375)	Denosumab (n = 403)	Placebo (n = 93)	Denosumab (n = 92)
All Fracture Adverse Events	6 (1.6%)	3 (0.7%)	5 (5.6%)	12 (12.5%)
Osteoporotic Nonvertebral Fractures	4 (1.1%)	2 (0.5%)	5 (5.6%)	9 (9.4%)
Vertebral Fractures	1 (0.3%)	1 (0.2%)	0 (0%)	3 (3.3%)

^a Interim analysis of safety data from the start of the safety follow-up phase through 02 December 2008

Source: 120-day Safety Update and 20040135 CSR

7. Clinical Safety of Denosumab

7.1 Key Points

- The PMO and HALT Combined Safety Analysis Set encompassed approximately 13,000 patient-years of exposure to denosumab (approximately 11,000 patient years for PMO and 2,000 patient-years for HALT) with similar exposure to placebo. Subjects were exposed to denosumab for up to 5 years. Open-label data will be collected from the ongoing clinical trials for up to 10 years of total exposure to denosumab for further evaluation of safety.
- Denosumab administered SC was generally well tolerated with injection-site reaction incidence similar to placebo (< 1%).
- Denosumab caused transient and mild decreases in serum calcium that were generally within the normal range and asymptomatic. All subjects in the phase 3 and ongoing studies received or will receive calcium and vitamin D supplementation.
- In women with PMO, more subjects in the denosumab group experienced skin infections requiring hospitalization (0.4% denosumab, 0.1% placebo); events were primarily cellulitis. Overall, there were no differences in the incidences of adverse events of infections, including opportunistic infections, between denosumab- and placebo-treated subjects in the PMO and HALT pivotal studies. The incidences of most infections reported as serious adverse events (SAEs) were balanced indicating no generalized increase in the risk of SAEs of infection.
- In men with prostate cancer receiving ADT, more subjects in the denosumab group experienced adverse events of cataracts (4.7% denosumab, 1.2% placebo). There were no differences in the incidences of adverse events of cataracts between denosumab- and placebo-treated subjects in the PMO pivotal studies (5.8%, 6.3%) and in women with breast cancer receiving aromatase inhibitor therapy (AIT) (0.8%, 0.8%).
- In the PMO and HALT programs, no adverse events were confirmed by an external, independent adjudication as osteonecrosis of the jaw (ONJ).
- The incidences of cardiovascular events, fracture healing complications, malignancies, and drug hypersensitivity reactions were specifically identified as adverse events of interest and were similar in the denosumab and placebo groups.
- No antibodies that neutralize denosumab have been observed.
- The number of deaths was balanced in the denosumab and placebo groups.

7.2 Exposure to Denosumab

In clinical studies included in the BLA, 7848 subjects received at least 1 dose of denosumab and 5199 subjects received placebo. An additional 916 subjects received alendronate in key active-controlled denosumab studies in the PMO setting. A total of 5655 subjects were treated with denosumab in the phase 2 and 3 PMO studies, and 860 subjects were treated with denosumab in the phase 3 HALT studies. A total of

4016 subjects were treated with denosumab for ≥ 3 years, and 113 subjects were treated with denosumab for ≥ 5 years. The PMO and HALT Combined Safety Analysis Set encompassed approximately 13,000 patient-years of exposure to denosumab (approximately 11,000 patient-years for PMO and 2,000 patient-years for HALT) with similar exposure to matching placebo.

The size of the denosumab clinical program provided 80% power to detect a 2-fold increase in background events occurring at a rate of 4/1000 or higher.

7.3 Assessment of Safety

Throughout the clinical development program, safety was evaluated through the collection of all treatment-emergent adverse events, including SAEs, and subsequent assessment of the severity, relationship to treatment, onset, duration, and outcome of the adverse events. Hematology, serum chemistry, electrocardiogram (ECG), and vital signs measurements (heart rate, systolic and diastolic blood pressure) were assessed at regular intervals. Central laboratories were used to provide uniform measurement of the key hematology and chemistry parameters used in the analyses of safety. In addition, subject safety was monitored on an ongoing basis throughout the pivotal trials by an external, independent Data Monitoring Committee (DMC); separate external, independent adjudication committees reviewed cardiovascular SAEs (Studies 20030216 and 20040138 only) and potential cases of ONJ.

The safety analysis population consisted of all subjects who received at least 1 dose of investigational product.

An integrated analysis of adverse events (including adverse events, SAEs, fatal adverse events, adverse events leading to withdrawal from investigational product, and adverse events leading to withdrawal from study) was performed, focused primarily on data from 4 key, placebo-controlled studies: treatment of PMO fracture study (20030216, $n = 7762$ treated subjects), prevention of PMO study (20040132, $n = 329$ treated subjects), HALT breast cancer study (20040135, $n = 249$ treated subjects), and HALT prostate cancer study (20040138, $n = 1456$ treated subjects).

Data from Studies 20030216 and 20040132 were integrated to form the Primary PMO Safety Analysis Set, which comprises investigational product exposure of 11140.5 patient-years for denosumab and 11028.7 patient-years for placebo, with a mean (SD) per-subject cumulative exposure of approximately 2.75 (0.65) years for the denosumab group (with matched placebo exposure of 2.73 [0.66] years). Data from

Studies 20040135 and 20040138 form the Primary HALT Safety Analysis Set, which comprises investigational product exposure of 2095.3 patient-years for denosumab and 1985.7 patient-years for placebo, with a mean (SD) per-subject cumulative exposure of approximately 2.44 (0.81) years for the denosumab group (with matched placebo exposure of 2.35 [0.87] years). In addition, analyses of adverse events of interest were performed using an integrated dataset from all 4 studies across both population subsets (Studies 20030216, 20040132, 20040138, and 20040135).

The sections below present safety information, including adverse events, deaths, SAEs ([Section 7.4](#)), as well as summaries of specific safety assessments that were predefined or analyzed in response to safety findings in the denosumab development program, performed per regulatory agency request, or conducted because analyses were reported in the regulatory applications for marketed antiresorptive agents (ie, bisphosphonates). For simplicity in this document, the safety discussions below will focus primarily on the integrated analysis set that combines the Primary PMO and Primary HALT Safety Analysis Sets.

7.4 Overall Adverse Events

Denosumab was generally well tolerated in all clinical studies, with a comparable incidence of adverse events overall between the denosumab and placebo or active-comparator treatment groups and a low incidence of treatment-related adverse events, SAEs, withdrawals due to adverse events, and deaths reported in every study evaluated to date ([Table 16](#) and [Table 17](#)). Most adverse events were mild to moderate, transient, and considered unrelated to denosumab. Approximately 5% to 6% permanently discontinued investigational product due to adverse events, with no notable difference in the incidence of such withdrawals between denosumab and placebo groups. Few adverse events leading to investigational product discontinuation or study withdrawal were attributed to investigational product (< 1% incidence in both treatment groups).

**Table 16. Summary of Subject Incidence of Adverse Events
(Primary PMO Safety Analysis Set)**

Adverse Events	Study 20040132		Study 20030216		Overall	
	Placebo (N=165) n (%)	Denosumab 60 mg Q6M (N=164) n (%)	Placebo (N=3876) n (%)	Denosumab 60 mg Q6M (N=3886) n (%)	Placebo (N=4041) n (%)	Denosumab 60 mg Q6M (N=4050) n (%)
All	157 (95.2)	156 (95.1)	3607 (93.1)	3605 (92.8)	3764 (93.1)	3761 (92.9)
Serious	9 (5.5)	19 (11.6)	972 (25.1)	1004 (25.8)	981 (24.3)	1023 (25.3)
Fatal	0 (0.0)	0 (0.0)	90 (2.3)	70 (1.8)	90 (2.2)	70 (1.7)
Leading to Study Discontinuation	2 (1.2)	1 (0.6)	81 (2.1)	93 (2.4)	83 (2.1)	94 (2.3)
Leading to Investigational Product Discontinuation	6 (3.6)	5 (3.0)	202 (5.2)	192 (4.9)	208 (5.1)	197 (4.9)

N = Number of subjects who received ≥ 1 dose of investigational product
Includes only treatment-emergent adverse events
Source: Summary of Clinical Safety (SCS)

**Table 17. Summary of Subject Incidence of Adverse Events
(Primary HALT Safety Analysis Set)**

Adverse Events	Study 20040135		Study 20040138		Overall	
	Placebo (N=120) n (%)	Denosumab 60 mg Q6M (N=129) n (%)	Placebo (N=725) n (%)	Denosumab 60 mg Q6M (N=731) n (%)	Placebo (N=845) n (%)	Denosumab 60 mg Q6M (N=860) n (%)
All	108 (90.0)	117 (90.7)	627 (86.5)	638 (87.3)	735 (87.0)	755 (87.8)
Serious	11 (9.2)	19 (14.7)	222 (30.6)	253 (34.6)	233 (27.6)	272 (31.6)
Fatal	1 (0.8)	1 (0.8)	46 (6.3)	44 (6.0)	47 (5.6)	45 (5.2)
Leading to Study Discontinuation	5 (4.2)	1 (0.8)	44 (6.1)	51 (7.0)	49 (5.8)	52 (6.0)
Leading to Investigational Product Discontinuation	5 (4.2)	2 (1.6)	47 (6.5)	49 (6.7)	52 (6.2)	51 (5.9)

N = Number of subjects who received ≥ 1 dose of investigational product
Includes only treatment-emergent adverse events
Source: SCS

7.4.1 Deaths

Deaths were infrequent in all studies included in the BLA. In the Primary PMO Safety Analysis Set, 70 subjects (1.7%) in the denosumab group and 90 subjects (2.2%) in the placebo group had a fatal adverse event during study participation or within 6 months of the last administration of investigational product (all deaths in this analysis set occurred in the treatment of PMO fracture study [20030216]). Fatal adverse events were reported as potentially related to investigational product in 5 subjects (0.1%) in the denosumab group and 1 subject (< 0.1%) in the placebo group. Treatment-related fatal adverse events in the denosumab group included cerebellar tumor (event onset at study day

843), myocardial infarction (event onset at study day 1091), ovarian cancer (event onset at study day 769), pancreatitis (event onset at study day 752), and acute pancreatitis in association with gallstones (event onset unknown). The treatment-related fatal adverse event in the placebo group was adenocarcinoma (event onset at study day 304).

In the Primary HALT Safety Analysis Set, 45 subjects (5.2%) in the denosumab group and 47 subjects (5.6%) in the placebo group had a fatal adverse event during study participation or within 6 months of the last administration of investigational product. No fatal adverse event in the denosumab group was considered potentially related to investigational product. In the HALT prostate cancer study (20040138), 1 fatal adverse event due to cardiovascular disorder was reported in the placebo group; the investigator reported the event to be potentially related to investigational product (event onset at study day 629).

Death rates overall were consistent with the expected rates for subjects with advanced age and the underlying disease processes (osteoporosis, cancer) of the populations examined, and no pattern was apparent in the types of fatal adverse events suggestive of a causative role for denosumab or any comparator.

7.4.2 Serious Adverse Events

Overall in the Primary PMO Safety Analysis Set, the subject incidence of SAEs was 25.3% in the denosumab group and 24.3% in the placebo group ([Table 18](#)). The types of SAEs reported were consistent with those generally expected for a population of advanced age.

Table 18. Serious Adverse Events With Incidence $\geq 0.5\%$ in Either Overall Group in the Primary PMO Safety Analysis Set, by Preferred Term in Descending Order of Frequency

Preferred Term	Study 20040132		Study 20030216		Overall	
	Placebo	Denosumab	Placebo	Denosumab	Placebo	Denosumab
	(N=165)	60 mg Q6M	(N=3876)	60 mg Q6M	(N=4041)	60 mg Q6M
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of subjects reporting SAEs ^a	9 (5.5)	19 (11.6)	972 (25.1)	1004 (25.8)	981 (24.3)	1023 (25.3)
Osteoarthritis	0 (0.0)	3 (1.8)	79 (2.0)	63 (1.6)	79 (2.0)	66 (1.6)
Pneumonia	0 (0.0)	3 (1.8)	36 (0.9)	34 (0.9)	36 (0.9)	37 (0.9)
Atrial fibrillation	0 (0.0)	0 (0.0)	33 (0.9)	36 (0.9)	33 (0.8)	36 (0.9)
Breast cancer	0 (0.0)	0 (0.0)	25 (0.6)	34 (0.9)	25 (0.6)	34 (0.8)
Angina pectoris	0 (0.0)	0 (0.0)	18 (0.5)	33 (0.8)	18 (0.4)	33 (0.8)
Cerebrovascular accident	0 (0.0)	0 (0.0)	23 (0.6)	32 (0.8)	23 (0.6)	32 (0.8)
Myocardial infarction	0 (0.0)	0 (0.0)	23 (0.6)	25 (0.6)	23 (0.6)	25 (0.6)
Radius fracture	0 (0.0)	0 (0.0)	23 (0.6)	25 (0.6)	23 (0.6)	25 (0.6)
Cataract	0 (0.0)	0 (0.0)	28 (0.7)	21 (0.5)	28 (0.7)	21 (0.5)
Back pain	0 (0.0)	0 (0.0)	20 (0.5)	20 (0.5)	20 (0.5)	20 (0.5)
Hypertension	0 (0.0)	0 (0.0)	22 (0.6)	19 (0.5)	22 (0.5)	19 (0.5)
Femur fracture	0 (0.0)	0 (0.0)	28 (0.7)	14 (0.4)	28 (0.7)	14 (0.3)
Femoral neck fracture	0 (0.0)	0 (0.0)	20 (0.5)	13 (0.3)	20 (0.5)	13 (0.3)

N = Number of subjects who received ≥ 1 dose of investigational product

n = Number of subjects reporting ≥ 1 event

Includes only treatment-emergent adverse events

Preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 11.0.

^a "Number of subjects reporting SAEs" includes all SAEs, regardless of incidence.

Source: Integrated Analysis of Safety (IAS)

Overall in the Primary HALT Safety Analysis Set, the incidence of SAEs was 31.6% in the denosumab group and 27.6% in the placebo group (Table 19). The types of SAEs reported were consistent with those generally expected for a population of advanced age and cancer medical history.

Table 19. Serious Adverse Events With Incidence $\geq 1\%$ in Either Overall Group in the Primary HALT Safety Analysis Set, by Preferred Term in Descending Order of Frequency

Preferred Term	Study 20040135		Study 20040138		Overall	
	Placebo	Denosumab	Placebo	Denosumab	Placebo	Denosumab
	(N=120)	60 mg Q6M	(N=725)	60 mg Q6M	(N=845)	60 mg Q6M
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of subjects reporting SAEs ^a	11 (9.2)	19 (14.7)	222 (30.6)	253 (34.6)	233 (27.6)	272 (31.6)
Myocardial infarction	0 (0.0)	1 (0.8)	18 (2.5)	14 (1.9)	18 (2.1)	15 (1.7)
Pneumonia	1 (0.8)	0 (0.0)	11 (1.5)	11 (1.5)	12 (1.4)	11 (1.3)
Atrial fibrillation	1 (0.8)	0 (0.0)	8 (1.1)	11 (1.5)	9 (1.1)	11 (1.3)
Cerebrovascular accident	0 (0.0)	0 (0.0)	12 (1.7)	10 (1.4)	12 (1.4)	10 (1.2)
Transient ischaemic attack	1 (0.8)	1 (0.8)	4 (0.6)	9 (1.2)	5 (0.6)	10 (1.2)
Coronary artery disease	0 (0.0)	0 (0.0)	11 (1.5)	9 (1.2)	11 (1.3)	9 (1.0)
Cardiac failure congestive	1 (0.8)	0 (0.0)	10 (1.4)	6 (0.8)	11 (1.3)	6 (0.7)
Metastases to bone	1 (0.8)	0 (0.0)	10 (1.4)	3 (0.4)	11 (1.3)	3 (0.3)

N = Number of subjects who received ≥ 1 dose of investigational product

n = Number of subjects reporting ≥ 1 event

Includes only treatment-emergent adverse events

Preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 11.0.

^a "Number of subjects reporting SAEs" includes all SAEs, regardless of incidence.

Source: IAS

SAEs in prespecified adverse events of interest are discussed in [Section 7.5](#).

7.4.3 Most Common Adverse Events

The overall pattern and type of adverse events were generally similar between the PMO Safety Analysis Set ([Table 20](#)) and the HALT Safety Analysis set ([Table 21](#)) and were consistent with the advanced age of the populations. Adverse events were rarely (ie, approximately $\leq 1\%$ of subjects for any single event) attributed to investigational product administration.

Table 20. Adverse Events With Incidence \geq 5% in Either Overall Group in the Primary PMO Safety Analysis Set, by Preferred Term in Descending Order of Frequency

Preferred Term	Study 20040132		Study 20030216		Overall	
	Placebo (N=165) n (%)	Denosumab 60 mg Q6M (N=164) n (%)	Placebo (N=3876) n (%)	Denosumab 60 mg Q6M (N=3886) n (%)	Placebo (N=4041) n (%)	Denosumab 60 mg Q6M (N=4050) n (%)
Number of subjects reporting adverse events ^a	157 (95.2)	156 (95.1)	3607 (93.1)	3605 (92.8)	3764 (93.1)	3761 (92.9)
Back pain	34 (20.6)	33 (20.1)	1340 (34.6)	1347 (34.7)	1374 (34.0)	1380 (34.1)
Arthralgia	42 (25.5)	43 (26.2)	782 (20.2)	784 (20.2)	824 (20.4)	827 (20.4)
Hypertension	14 (8.5)	7 (4.3)	636 (16.4)	614 (15.8)	650 (16.1)	621 (15.3)
Nasopharyngitis	32 (19.4)	36 (22.0)	600 (15.5)	563 (14.5)	632 (15.6)	599 (14.8)
Pain in extremity	21 (12.7)	25 (15.2)	430 (11.1)	453 (11.7)	451 (11.2)	478 (11.8)
Osteoarthritis	5 (3.0)	4 (2.4)	442 (11.4)	436 (11.2)	447 (11.1)	440 (10.9)
Constipation	8 (4.8)	19 (11.6)	361 (9.3)	355 (9.1)	369 (9.1)	374 (9.2)
Influenza	20 (12.1)	15 (9.1)	335 (8.6)	331 (8.5)	355 (8.8)	346 (8.5)
Musculoskeletal pain	10 (6.1)	18 (11.0)	291 (7.5)	297 (7.6)	301 (7.4)	315 (7.8)
Bronchitis	8 (4.8)	6 (3.7)	301 (7.8)	301 (7.7)	309 (7.6)	307 (7.6)
Hypercholesterolaemia	4 (2.4)	5 (3.0)	236 (6.1)	280 (7.2)	240 (5.9)	285 (7.0)
Headache	19 (11.5)	26 (15.9)	258 (6.7)	237 (6.1)	277 (6.9)	263 (6.5)
Urinary tract infection	17 (10.3)	18 (11.0)	253 (6.5)	245 (6.3)	270 (6.7)	263 (6.5)
Diarrhoea	8 (4.8)	14 (8.5)	236 (6.1)	228 (5.9)	244 (6.0)	242 (6.0)
Cough	5 (3.0)	11 (6.7)	238 (6.1)	224 (5.8)	243 (6.0)	235 (5.8)
Cataract	0 (0.0)	4 (2.4)	253 (6.5)	229 (5.9)	253 (6.3)	233 (5.8)
Cystitis	3 (1.8)	4 (2.4)	225 (5.8)	228 (5.9)	228 (5.6)	232 (5.7)
Dizziness	9 (5.5)	7 (4.3)	218 (5.6)	217 (5.6)	227 (5.6)	224 (5.5)
Depression	7 (4.2)	10 (6.1)	221 (5.7)	213 (5.5)	228 (5.6)	223 (5.5)
Upper respiratory tract infection	22 (13.3)	21 (12.8)	167 (4.3)	190 (4.9)	189 (4.7)	211 (5.2)
Fall	6 (3.6)	1 (0.6)	250 (6.4)	205 (5.3)	256 (6.3)	206 (5.1)
Nausea	12 (7.3)	16 (9.8)	193 (5.0)	178 (4.6)	205 (5.1)	194 (4.8)
Dyspepsia	10 (6.1)	10 (6.1)	212 (5.5)	178 (4.6)	222 (5.5)	188 (4.6)

N = Number of subjects who received \geq 1 dose of investigational product

n = Number of subjects reporting \geq 1 event

Includes only treatment-emergent adverse events

Preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 11.0.

^a "Number of subjects reporting adverse events" includes all adverse events, regardless of incidence.

Source: IAS

Table 21. Adverse Events With Incidence $\geq 5\%$ in Either Overall Group in the Primary HALT Safety Analysis Set, by Preferred Term in Descending Order of Frequency

Preferred Term	Study 20040135		Study 20040138		Overall	
	Placebo (N=120) n (%)	Denosumab 60 mg Q6M (N=129) n (%)	Placebo (N=725) n (%)	Denosumab 60 mg Q6M (N=731) n (%)	Placebo (N=845) n (%)	Denosumab 60 mg Q6M (N=860) n (%)
Number of subjects reporting adverse events ^a	108 (90.0)	117 (90.7)	627 (86.5)	638 (87.3)	735 (87.0)	755 (87.8)
Arthralgia	30 (25.0)	31 (24.0)	80 (11.0)	92 (12.6)	110 (13.0)	123 (14.3)
Back pain	15 (12.5)	18 (14.0)	74 (10.2)	81 (11.1)	89 (10.5)	99 (11.5)
Constipation	11 (9.2)	15 (11.6)	75 (10.3)	73 (10.0)	86 (10.2)	88 (10.2)
Pain in extremity	14 (11.7)	19 (14.7)	51 (7.0)	66 (9.0)	65 (7.7)	85 (9.9)
Fatigue	17 (14.2)	17 (13.2)	45 (6.2)	44 (6.0)	62 (7.3)	61 (7.1)
Oedema peripheral	5 (4.2)	8 (6.2)	48 (6.6)	53 (7.3)	53 (6.3)	61 (7.1)
Hypertension	7 (5.8)	2 (1.6)	51 (7.0)	57 (7.8)	58 (6.9)	59 (6.9)
Musculoskeletal pain	6 (5.0)	11 (8.5)	26 (3.6)	41 (5.6)	32 (3.8)	52 (6.0)
Nasopharyngitis	4 (3.3)	4 (3.1)	45 (6.2)	47 (6.4)	49 (5.8)	51 (5.9)
Dizziness	4 (3.3)	5 (3.9)	31 (4.3)	41 (5.6)	35 (4.1)	46 (5.3)
Cough	5 (4.2)	13 (10.1)	27 (3.7)	33 (4.5)	32 (3.8)	46 (5.3)
Diarrhoea	9 (7.5)	5 (3.9)	39 (5.4)	40 (5.5)	48 (5.7)	45 (5.2)
Hot flush	8 (6.7)	7 (5.4)	32 (4.4)	38 (5.2)	40 (4.7)	45 (5.2)
Urinary tract infection	5 (4.2)	7 (5.4)	32 (4.4)	37 (5.1)	37 (4.4)	44 (5.1)

N = Number of subjects who received ≥ 1 dose of investigational product

n = Number of subjects reporting ≥ 1 event

Includes only treatment-emergent adverse events

Preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 11.0.

^a "Number of subjects reporting adverse events" includes all adverse events, regardless of incidence.

Source: IAS

7.4.4 Adverse Events With Differences Between Treatment Groups

Adverse events with differences between treatment groups were determined separately for the PMO population (pooled data from Studies 20030216 and 20040132) and the HALT population (pooled data from Studies 20040138 and 20040135). Within each of these pools, differences in "common" adverse events were defined as adverse events reported with (a) $\geq 2\%$ incidence in denosumab-treated subjects and (b) $\geq 1\%$ greater incidence in the denosumab-treated subjects than in the placebo-treated subjects, regardless of investigator attribution of relationship to denosumab.

“Less common” adverse events with differences between treatment groups were defined as adverse events (a) for which there is a theoretical plausibility, based upon the pharmacologic effects of RANKL inhibition, that they are causally related to denosumab and (b) that were reported with greater frequency in the denosumab-treated subjects than in the placebo-treated subjects. The only adverse event meeting this definition in the PMO population was skin infections leading to hospitalization. No adverse events met this definition in the HALT population.

Adverse events meeting these definitions are summarized in [Table 22](#).

Table 22. Summary of Denosumab Adverse Events

Population	Adverse Event	Placebo	Denosumab
PMO Analysis Set (Studies 20030216 & 20040132)	Hypercholesterolemia	5.9%	7.0%
	Eczema	1.7%	3.1%
	Skin infection leading to hospitalization	0.1%	0.4%
HALT Analysis Set (Studies 20040138 & 20040135)	Arthralgia	13.0%	14.3%
	Pain in extremity	7.7%	9.9%
	Musculoskeletal pain	3.8%	6.0%
	Dizziness	4.1%	5.3%
	Osteoarthritis	3.1%	4.3%
	Hypoesthesia	1.5%	2.7%
	Cataract ^a	1.2%	4.1%
	Urinary retention ^a	1.3%	2.8%
	Cough ^b	3.8%	5.3%
	Myalgia ^b	1.8%	2.8%

^a Difference observed in Study 20040138

^b Difference observed in Study 20040135

Source: SCS

7.5 Safety Assessments for Adverse Events of Interest

The adverse events discussed below were prespecified as adverse events of interest, with the exception of cataracts ([Section 7.5.6](#)) which was a finding from the HALT prostate cancer study (20040138).

7.5.1 Reduction of Serum Calcium and Hypocalcemia

Because denosumab inhibits osteoclast mediated bone resorption, it has the potential to lower serum calcium levels by decreasing mobilization of calcium from bone into the bloodstream.

Hypocalcemia adverse events and abnormalities of serum calcium were examined in detail in all denosumab clinical studies. In the phase 3 denosumab studies in PMO and HALT, calcium and vitamin D supplementation was mandated per protocol to reduce the risk of hypocalcemia and to maintain bone health. Denosumab administration was associated with mild (approximately 3% at the month 1 time point relative to baseline), transient decreases in serum calcium within the normal range that had no apparent clinical significance. The nadir for reductions in serum calcium occurred approximately 10 days after the first dose. Decreases in serum calcium to < 8.0 mg/dL were rare and of comparable incidence in the treatment groups in the pivotal studies ([Table 23](#)); and no denosumab-treated subjects and 1 placebo subject had decreases to < 7.0 mg/dL. Decreases in serum calcium observed with denosumab treatment were similar to those observed with alendronate treatment in the 2 head-to-head comparison studies (20050141 and 20050234).

Table 23. Decreases in Serum Calcium Corrected by Albumin Subject Incidences During the Studies in the Primary PMO and HALT Safety Analysis Sets

Serum Calcium (mg/dL)	PMO		HALT		Overall	
	Placebo (N=4041) n (%)	Denosumab (N=4050) n (%)	Placebo (N=845) n (%)	Denosumab (N=860) n (%)	Placebo (N=4886) n (%)	Denosumab (N=4910) n (%)
< LLN ^a - 8.0	10 (0.2)	61 (1.5)	5 (0.6)	24 (2.8)	15 (0.3)	85 (1.7)
< 8.0 – 7.5	3 (<0.1)	4 (<0.1)	1 (0.1)	3 (0.3)	4 (<0.1)	7 (0.1)
< 7.5	2 (<0.1)	2 (<0.1)	0 (0.0)	0 (0.0)	2 (<0.1)	2 (<0.1)

^a Lower limit of normal (LLN) is 8.5 mg/dL for primary PMO studies and 8.4 mg/dL for primary HALT studies.

Source: t1-07_004_006_lab_ca_cr_cuts_pmo.rtf, t1-07_004_007_lab_ca_cr_cuts_halt.rtf, and t1-07_004_008_lab_ca_cr_cuts_all.rtf,

There was no evidence of an association between decreased serum calcium values and adverse events pre-identified as manifestations of hypocalcemia (ie, paresthesia, oral paresthesia, hypoesthesia, oral hypoesthesia, and tetany); incidences of these events were balanced in denosumab and placebo groups.

In the PMO and bone loss due to HALT clinical programs, 1 subject receiving denosumab and no subjects receiving placebo had symptomatic hypocalcemia. A subject receiving denosumab in the HALT prostate cancer study (20040138) with concurrent pancreatic cancer experienced an SAE of hypocalcemia (serum calcium 7.0 mg/dL; this value was obtained at a local laboratory and therefore was not in the clinical database).

Patients with severe kidney disease or ESRD rely more heavily on bone to provide a source of calcium. This well-described feature of calcium homeostasis is a consequence of impaired abilities to re-absorb calcium from the urine and to absorb calcium in the gastrointestinal tract. Therefore, these patients may be more susceptible to reductions in serum calcium with antiresorptive therapy. Changes in serum calcium were analyzed by degree of kidney function in the ongoing extension study (20060289) of the treatment of PMO fracture study (20030216). Serum calcium was assessed at study day 10 (\pm 5 days) and analyzed by baseline creatinine clearance. Changes in serum calcium across the spectrum of kidney function were generally mild (Table 24). Although slightly larger reductions in serum calcium were observed in subjects with severe renal impairment, no adverse events associated with low serum calcium values were noted in any subject, regardless of renal function.

Table 24. Percent Change in Serum Calcium to Day 10 by Kidney Impairment Categories in Subjects Newly Exposed to Denosumab in the Extension Study (20060289) to the Treatment of PMO Fracture Study (20030216) (120-day Safety Update to Denosumab Bone Loss BLA)

	Kidney Impairment Categories (Estimated Serum Creatinine Clearance Range [mL/min])				
	Normal (\geq 90)	Mild (60 - < 90)	Moderate (30 - < 60)	Severe (15 - < 30)	ESRD (< 15)
n	198	1050	806	20	0
Median ^a	-3.2	-3.1	-3.1	-5.7	—
Q1, Q3	-6.2, 0.0	-6.1, 0.0	-6.1, 0.0	-7.4, -3.2	—

^a Median percent change in serum calcium concentration (corrected by albumin) from baseline to day 10 of the extension study (20060289).

ESRD = end-stage renal disease

Source: 120-day Safety Update

Changes in serum calcium also were analyzed by degree of kidney function in a phase 1, single-dose (60 mg SC) study in healthy subjects and subjects with varying degrees of renal function (20040245). The incidence of serum calcium < 7.5 mg/dL in subjects with severe kidney disease or end-stage renal disease (ESRD) was greater compared with those with mild or moderate kidney impairment and those with normal kidney function ([Table 25](#)).

**Table 25. Incidence of Serum Calcium < 7.5 mg/dL
(Study 20040245)**

	Kidney Impairment Categories (Estimated Serum Creatinine Clearance Range [mL/min])				
	Normal (≥ 90)	Mild (60 - < 90)	Moderate (30 - < 60)	Severe (15 - < 30)	ESRD (< 15)
N	12	13	13	9	8
n – subjects with serum calcium < 7.5 mg/dL	0	1	0	2	2

Source: 20040245 CSR

The proposed prescribing information recommends clinical monitoring of calcium levels in patients predisposed to hypocalcemia, including those with severe kidney impairment and those receiving dialysis.

7.5.2 Infections

RANKL and RANK are expressed on activated lymphocytes and dendritic cells, respectively. Therefore, RANK ligand inhibition was investigated nonclinically and clinically for any potential immune effect.

Nonclinical studies of OPG or denosumab in normal adult animals, including studies of denosumab lasting up to 16 months in cynomolgus monkeys, demonstrated that RANKL inhibition did not impair host response to infection, delayed-type hypersensitivity, or neoantigen challenge, and does not alter sensitive measures of immune system status (lymphoid organ weights and histology, basal immunoglobulin concentration, or peripheral lymphocyte counts) ([Stolina et al, 2008](#); [Miller et al, 2007](#); [Stolina et al, 2007](#); [Stolina et al, 2003](#)). As a whole, these findings indicate a normal integrated functioning of dendritic cells (and other antigen presenting cells), T cells, and B cells following inhibition of RANKL and suggest that RANKL is not uniquely required in the adult immune system for host resistance or immunosurveillance.

No clinically relevant effect of denosumab treatment was observed on peripheral blood immune cell subset profiles in studies in healthy, older men (Study 20030148), postmenopausal women (Studies 20010124, 20030164, and 20030180), and postmenopausal women with low bone mineral density (Study 20010223). No evidence of a treatment effect of denosumab on immunoglobulin production was observed (Studies 20010124, 20030148, 20030164, and 20030180).

Overall, in the clinical program to date, adverse events of infection were balanced between treatment groups. In the denosumab clinical program (Primary PMO and HALT Combined Safety Analysis Set), adverse events of infection (non-serious and serious events combined) were balanced (50.1% denosumab, 50.6% placebo). The incidence of SAEs of infection in the Primary PMO and HALT Combined Safety Analysis Set was 4.3% in the denosumab group and 3.4% in the placebo group ([Table 26](#)). Opportunistic infections were rare (approximately 0.1%) and were balanced between treatment groups. Discontinuations from investigational product due to adverse events of infection were balanced between treatment groups (PMO: 0.2% [7 subjects] denosumab, 0.1% [6] placebo; HALT: 0% denosumab, 0.2% [2] placebo). Fatal adverse events of infection were balanced between the treatment groups in the Primary PMO Safety Analysis Set (6 subjects denosumab [0.1%], 6 subjects placebo [0.1%]). Fatal adverse events of infection occurred only in the placebo group in the Primary HALT Safety Analysis Set (0 subjects denosumab, 6 subjects placebo [0.7%]).

The majority of the numeric imbalance in the incidence of infections reported as SAEs (4.3% in the denosumab group and 3.4% in the placebo group) was accounted for by events of cellulitis/erysipelas, diverticulitis, and cystitis/urinary tract infection ([Table 26](#)). The incidence of SAEs of possible opportunistic infections including tuberculosis and invasive fungal infections was low overall and balanced between treatments (0.1% in both denosumab and placebo groups).

Table 26. Serious Adverse Events of Infection (Incidence > 0.1% in Either Overall Group) (Primary PMO and HALT Combined Safety Analysis Set)

Preferred Term	PMO		HALT		Overall	
	Placebo (N=4041) n (%)	Denosumab 60 mg Q6M (N=4050) n (%)	Placebo (N=845) n (%)	Denosumab 60 mg Q6M (N=860) n (%)	Placebo (N=4886) n (%)	Denosumab 60 mg Q6M (N=4910) n (%)
SAEs of infection	134 (3.3)	167 (4.1)	34 (4.0)	46 (5.3)	168 (3.4)	213 (4.3)
Pneumonia	36 (0.9)	37 (0.9)	12 (1.4)	11 (1.3)	48 (1.0)	48 (1.0)
Urinary tract infection	10 (0.2)	17 (0.4)	3 (0.4)	0 (0.0)	13 (0.3)	17 (0.3)
Diverticulitis	6 (0.1)	10 (0.2)	0 (0.0)	6 (0.7)	6 (0.1)	16 (0.3)
Gastroenteritis	7 (0.2)	9 (0.2)	2 (0.2)	1 (0.1)	9 (0.2)	10 (0.2)
Cellulitis	1 (<0.1)	7 (0.2)	4 (0.5)	3 (0.3)	5 (0.1)	10 (0.2)
Appendicitis	7 (0.2)	8 (0.2)	1 (0.1)	1 (0.1)	8 (0.2)	9 (0.2)
Cystitis	2 (<0.1)	6 (0.1)	0 (0.0)	2 (0.2)	2 (<0.1)	8 (0.2)
Erysipelas	0 (0.0)	7 (0.2)	1 (0.1)	1 (0.1)	1 (<0.1)	8 (0.2)
Bronchitis	7 (0.2)	4 (0.1)	2 (0.2)	2 (0.2)	9 (0.2)	6 (0.1)
Bronchopneumonia	7 (0.2)	6 (0.1)	1 (0.1)	0 (0.0)	8 (0.2)	6 (0.1)
Sepsis	4 (0.1)	5 (0.1)	4 (0.5)	0 (0.0)	8 (0.2)	5 (0.1)

SAE = serious adverse event

Source: IAS

For the events of cellulitis/erysipelas, diverticulitis, and cystitis/urinary tract infection, a detailed clinical review was performed, as described below.

With respect to diverticulitis, a detailed clinical review of serious adverse event reports of diverticulitis and its complications showed that, overall, these events were relatively balanced between treatment groups ([Table 27](#)). Cases in the table included only those with clear evidence of diverticular infection based on clinical review.

**Table 27. Serious Adverse Events of Diverticulitis Based on Clinical Review
(Primary PMO and HALT Combined Safety Analysis Set)**

	PMO		HALT		Overall	
	Placebo (N=4041)	Denosumab 60 mg Q6M (N=4050)	Placebo (N=845)	Denosumab 60 mg Q6M (N=860)	Placebo (N=4886)	Denosumab 60 mg Q6M (N=4910)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Aggregate Diverticulitis SAEs ^a	8 (0.2)	12 (0.3)	3 (0.4)	6 (0.7)	11 (0.2)	18 (0.4)
Diverticulitis	6 (0.1)	10 (0.2)	0 (0.0)	6 (0.7)	6 (0.1)	16 (0.3)
Diverticulum	1 (<0.1)	2 (<0.1)	1 (0.1)	0 (0.0)	2 (<0.1)	2 (<0.1)
Diverticulum intestinal	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Enterovesical fistula	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	2 (<0.1)	0 (0.0)

^a Aggregate diverticulitis includes terms that revealed an underlying etiology of diverticulitis with manual case review.

Source: IAS

Although numeric imbalances in urinary tract infection and cystitis were observed, the aggregate incidence of SAEs of infections relating to the urinary tract was relatively balanced in denosumab and placebo groups ([Table 28](#)).

**Table 28. Serious Adverse Events of Infections of the Urinary Tract
(Primary PMO and HALT Combined Safety Analysis Set)**

	Placebo (N=4041) n (%)	Denosumab 60 mg Q6M (N=4050) n (%)	Placebo (N=845) n (%)	Denosumab 60 mg Q6M (N=860) n (%)	Placebo (N=4886) n (%)	Denosumab 60 mg Q6M (N=4910) n (%)
Aggregate Infections of the Urinary Tract SAEs	20 (0.5)	30 (0.7)	5 (0.6)	5 (0.6)	25 (0.5)	35 (0.7)
Urinary tract infection	10 (0.2)	17 (0.4)	3 (0.4)	0 (0.0)	13 (0.3)	17 (0.3)
Cystitis	2 (<0.1)	6 (0.1)	0 (0.0)	2 (0.2)	2 (<0.1)	8 (0.2)
Pyelonephritis	2 (<0.1)	6 (0.1)	0 (0.0)	0 (0.0)	2 (<0.1)	6 (0.1)
Urosepsis	2 (<0.1)	1 (<0.1)	2 (0.2)	3 (0.3)	4 (0.1)	4 (0.1)
Pyelonephritis acute	1 (<0.1)	1 (<0.1)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)
Pseudomonas infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (<0.1)
Pyelonephritis chronic	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Escherichia infection	2 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)	0 (0.0)
Bacterial pyelonephritis	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Kidney infection	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Renal abscess	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)

Source: IAS

Skin infection adverse events were balanced between treatment groups (1.4% denosumab, 1.3% placebo). Although the incidence of SAEs for skin infection was low, an imbalance, primarily in cellulitis, was observed in the PMO studies (20030216 and 20040132 combined) (0.4% denosumab, 0.1% placebo) ([Table 29](#)). This imbalance was not observed in the HALT analysis set. The events of skin infections reported as SAEs were predominantly localized cellulitis of the lower extremities. Subjects who reported these events typically had pre-existing risk factors for cellulitis, including peripheral vascular disease, venous ulcers, and skin wounds. No consistent relationship to duration of treatment or time since last dose was noted. Treatment generally included short hospitalization and single-course antibiotics. No increased rate of denosumab discontinuation due to skin infections was noted. Subjects recovered fully and did not have recurrent infection despite persistent RANKL inhibition with 1 exception: a subject with grade IV pancreatic neuroendocrine carcinoma with penetration to ventricle and spleen experienced a fatal adverse event of cellulitis (bacteriological investigation of autopsy samples – *Streptococcus pyogenes*), complicated by sepsis, septic shock, and

multiple organ failure, which was considered by the investigator to be unrelated to denosumab.

**Table 29. Serious Adverse Events of Skin Infections
(Primary PMO and HALT Combined Safety Analysis Set)**

	PMO		HALT		Overall	
	Placebo (N=4041) n (%)	Denosumab (N=4050) n (%)	Placebo (N=845) n (%)	Denosumab (N=860) n (%)	Placebo (N=4886) n (%)	Denosumab (N=4910) n (%)
Aggregate Skin Infection SAEs	3 (0.1)	16 (0.4)	5 (0.6)	5 (0.6)	8 (0.2)	21 (0.4)
Cellulitis	1 (<0.1)	7 (0.2)	4 (0.5)	3 (0.3)	5 (0.1)	10 (0.2)
Erysipelas	0 (0)	7 (0.2)	1 (0.1)	1 (0.1)	1 (<0.1)	8 (0.2)
Infected Skin Ulcer	0 (0)	1 (<0.1)	0 (0)	1 (0.1)	0 (0)	2 (< 0.1)
Skin Bacterial Infection	0 (0)	2 (<0.1)	0 (0)	0 (0)	0 (0)	2 (<0.1)
Staphylococcal Infection	1 (<0.1)	1 (<0.1)	0 (0)	0 (0)	1 (<0.1)	1 (<0.1)
Subcutaneous Abscess	1 (<0.1)	0 (0)	0 (0)	0 (0)	1 (<0.1)	0 (0)

Source: IAS

There is no evidence from numerous nonclinical and clinical studies that denosumab is broadly or locally immunosuppressive. When examined in depth clinically, the imbalances in SAEs of diverticulitis and infections of the urinary tract are small and may be due to random variability.

The biologic mechanism by which RANKL inhibition might increase the risk of serious skin infections is unclear. Although numerous nonclinical studies have consistently shown no effect of RANKL inhibition on immune stimulation or suppression, 2 reports in nonclinical studies suggest that keratinocytes in mice can express RANKL under certain conditions ([Loser et al, 2006](#); [Yamaguchi and Sakaguchi, 2006](#)). These data suggest that RANKL may play an immunosuppressive role in skin; this would predict that inhibition of RANKL would increase immune responsiveness in skin. The relevance of these results to humans is unknown. In the absence of increased overall infection rates of skin infections, the finding of more hospitalizations in denosumab-treated patients with skin infections is difficult to interpret and causality cannot be confirmed or excluded. This safety finding can be appropriately managed through product labeling and continued risk assessment through the pharmacovigilance program.

7.5.3 Hypersensitivity

Any monoclonal antibody injected into humans could theoretically be associated with hypersensitivity reactions, including anaphylactic or anaphylactoid events, and many antibodies have been observed to elicit such reactions (eg, cetuximab). Thus, a conservative approach was taken to evaluate the potential for denosumab to result in allergic reactions and to characterize the timing, severity, and outcomes of any such reactions.

No evidence of an increased risk of hypersensitivity, drug hypersensitivity, or drug allergy reactions to denosumab has been demonstrated in clinical trials. Furthermore, events identified using standardized medical query (SMQ) narrow searches to analyze potential clinical consequences of hypersensitivity (listed in [Appendix 4](#)) demonstrated that denosumab did not pose an increased risk for clinical consequences of hypersensitivity reactions.

Few subjects reported adverse events associated with the administration site (eg, injection site pain, erythema, hematoma, pruritus, or irritation) in the Primary PMO Safety Analysis Set ($\leq 1\%$ in both treatment groups) and in the Primary HALT Safety Analysis Set (approximately 1% in both treatment groups).

7.5.4 Immunogenicity

Administration of any therapeutic protein has the potential to elicit an immune response against the protein. This immune response can result in the formation of antibodies which may neutralize the action of the molecule and may manifest as decreased or loss of efficacy. Immunogenicity testing (using validated assays) has been performed in all denosumab clinical studies. More than 13,000 subjects have been tested for antidenosumab antibodies in studies described in this marketing application, including > 8000 subjects who have received at least 1 dose of denosumab. In the clinical studies, samples for immunogenicity testing were collected before the first dose, at least every 6 months (for most studies), and at the end of study visit.

No antibodies which neutralize denosumab have been observed to date in the denosumab clinical development program.

7.5.5 Osteonecrosis of the Jaw

ONJ is defined as a lesion occurring in the oral cavity as an area of exposed alveolar or palatal bone where gingival or alveolar mucosa is normally found, associated with

nonhealing after appropriate care by 8 weeks in a patient without prior history of radiation to the head, face, or mouth ([Khosla et al, 2007](#)).

Bisphosphonate use has been associated with ONJ, particularly following tooth extraction and oral surgical procedures ([Ruggiero et al, 2004](#); [Marx, 2003](#)). ONJ has been reported in patients receiving high-dose IV bisphosphonate therapy for the treatment of advanced cancer and rarely in women with PMO. Hypothesized mechanisms for bisphosphonates include interference with bone remodeling and direct toxic effects on oral mucosa ([Reid, 2009](#); [Van den Wyngaert et al, 2006](#); [Marx et al, 2007](#); [Hansen et al, 2006](#)).

Based on the antiresorptive activities of denosumab, all denosumab clinical studies have been proactively monitored to detect potential events of ONJ since August 2007, and any potential events were adjudicated by an external, independent adjudication committee. The process comprises the following elements:

- specific search criteria to detect maxillofacial events which might be indicative of ONJ ([Appendix 5](#));
- collection of available information from investigators on all predefined oral events as well as those specifically reported as ONJ; and
- review and assessment of all these events by an external, independent adjudication committee in a blinded manner to determine whether the predefined criteria for ONJ were met.

No cases of ONJ have been identified in any ongoing or completed studies of subjects with PMO or bone loss due to HALT, the indications being sought in the BLA, using this methodology and adjudication process.

The ongoing cancer program evaluating patients with advanced cancer, including patients with breast or prostate cancer or multiple myeloma (see [Table 5](#) for populations and study designs) compares denosumab (120 mg Q4W SC, ie, approximately 12-fold greater than the dose used in the PMO and HALT studies) to zoledronic acid (4 mg IV Q4W) for the prevention of skeletal-related events. Two ONJ adverse events were reported in subjects receiving denosumab in advanced cancer open-label studies; in an ongoing, blinded study, 1 ONJ adverse event was reported in a subject receiving denosumab whose treatment assignment was unblinded. Two of these 3 subjects had prior exposure to IV bisphosphonates.

Assessment of ONJ will continue in ongoing clinical trials and in the pharmacovigilance program.

Recently, results of the ONJ adjudication process (described above) have become available from an advanced cancer study in patients with breast cancer and bone metastases (Study 20050136 [Table 5]). This was a phase 3, randomized, double-blind study comparing denosumab (120 mg Q4W SC) to zoledronic acid (4 mg Q4W IV) for the treatment of patients with advanced breast cancer and bone metastases. There was no statistically significant difference in the rate of ONJ between the 2 treatment arms. Complete analyses of the results from this study, and other advanced cancer studies, will be reported in a separate BLA.

7.5.6 Cataracts in Men With Prostate Cancer Receiving ADT

An imbalance in the incidence of adverse events of cataracts (including new diagnoses, worsening of existing cataracts, and cataract extractions) was noted in the 3-year pivotal study (20040138) in patients with prostate cancer receiving ADT (4.7% in the denosumab group and 1.2% in the placebo group). Many of these events occurred in subjects with a reported history of cataracts or were reported as worsening cataracts or lens extractions. The majority of subjects with this adverse event had events that occurred within the first year of study, and by the third year of study, the incidence rate in the denosumab group was similar to the placebo rate, suggesting that the risk did not increase with prolonged exposure. The reported prevalence rate of cataracts in men in the US population is > 40% in those 70 to 79 years old, and almost 70% in those \geq 80 years old (National Eye Institute, 2008), which is higher than that observed in this study. It is possible that the imbalance observed in Study 20040138 is a chance finding.

No imbalances in the incidence of cataracts were observed in a population of similar age (treatment of PMO fracture study [20030216]: 5.9% denosumab, 6.5% placebo) or in another population also receiving HALT (HALT breast cancer study [20040135]: 0.8% in both treatment groups). In addition, studies in monkeys using high doses of denosumab for up to 12 months noted no increase in the incidence of cataracts as assessed by slit-lamp ophthalmoscopy and histopathology.

Overall, the results across the bone loss program do not establish a relationship between denosumab and the development of cataracts. The incidence of cataracts was

balanced in the large PMO safety dataset (5.8% denosumab, 6.3% placebo). Available information provides no plausible mechanism linking denosumab to cataracts. However, given the imbalance observed, the incidence of cataracts will continue to be monitored in ongoing studies as well as in a randomized, placebo-controlled study specifically designed to assess this risk in the prostate cancer population receiving ADT ([Section 8](#)).

7.5.7 Cardiovascular Safety

The role of RANKL inhibition in vascular biology is unknown, and the published literature is conflicting. In epidemiological studies, higher levels of OPG were associated with higher cardiovascular risk and with a variety of cardiovascular and atherosclerosis risk factors, including older age, diabetes, and hypertension ([Hofbauer and Schoppet, 2004](#); [Kudlacek et al, 2003](#); [Ueland et al, 2004](#); [Browner et al, 2001](#)). However, causality can not be determined because these observational studies were cross-sectional. By contrast, multiple animal models suggest a protective effect for OPG in arterial biology. Transgenic inactivation of OPG (OPG knockout mice) results in medial arterial calcification ([Bucay et al, 1998](#)), and transgenic overexpression of soluble OPG inhibits medial artery calcification in these mice ([Min et al, 2000](#)). OPG inactivation accelerates atherosclerotic lesion progression and calcification in a mouse model of atherosclerosis ([Bennett et al, 2006](#)). In interventional studies, OPG inhibits vascular calcification in a mouse model of atherosclerosis ([Morony et al, 2008](#)) and in rats with atherosclerosis induced by warfarin and vitamin D ([Price et al, 2001](#)). Because of the theoretical role RANKL might play in vascular biology, cardiovascular safety was examined in detail in the denosumab nonclinical and clinical programs.

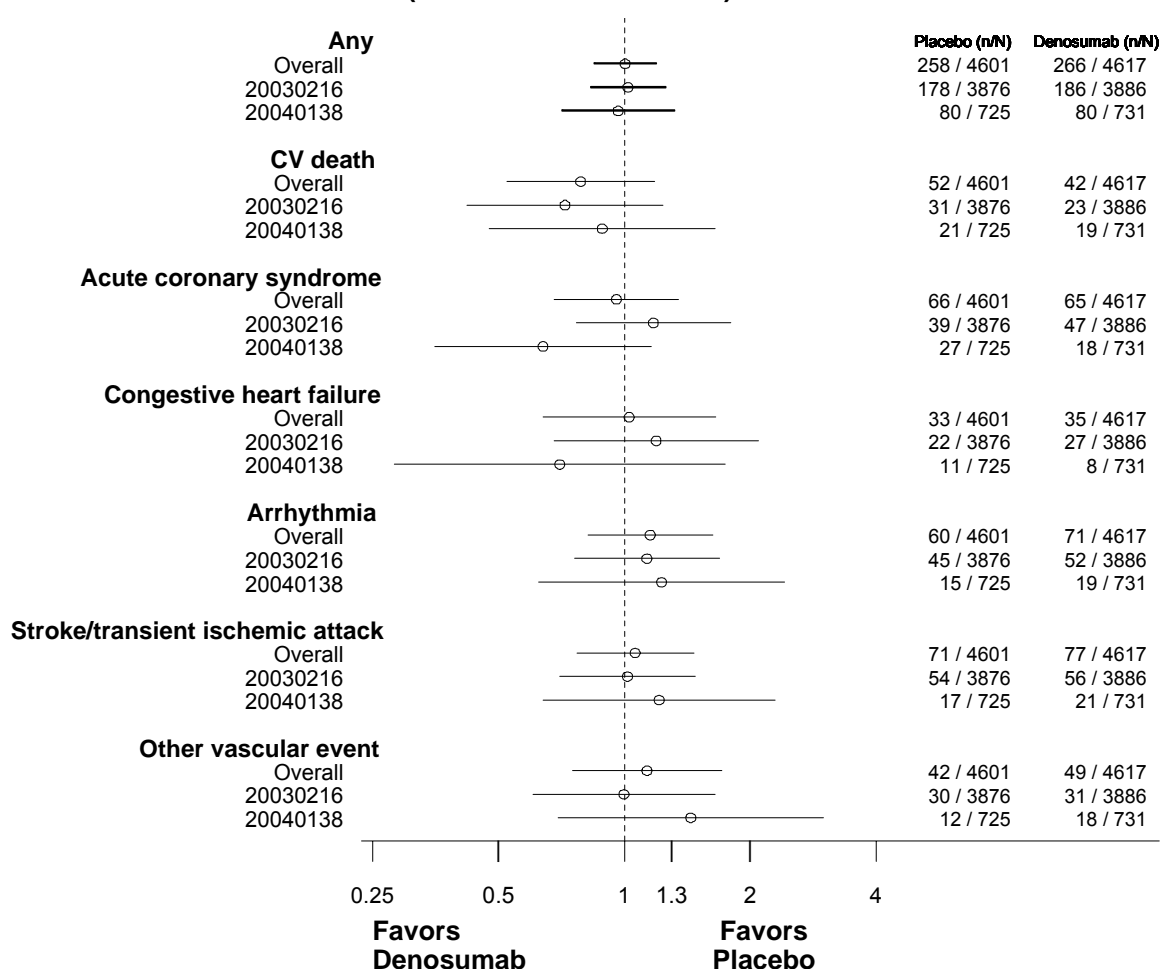
No evidence of cardiovascular toxicity has been demonstrated in nonclinical studies of denosumab across a comprehensive panel of evaluations.

In clinical trials, extensive evaluations of cardiovascular data have been completed, including cardiovascular adverse events and SAEs; external, independent adjudication of cardiovascular SAEs; and ECGs, including QTc effects. In addition, in the treatment of PMO fracture study (20030216), aortic calcification was assessed by lateral spine x-rays in a subset of subjects considered at high cardiovascular risk based on the modified Raloxifene Use for the Heart (RUTH) criteria used in the Multiple Outcomes of Raloxifene (MORE) study ([Keech et al, 2005](#)).

No differences between treatment groups were observed in the incidence of cardiac or vascular disorders adverse events. No differences relative to placebo were observed in the subject incidence of positively adjudicated cardiovascular SAEs (ie, events that were

reviewed and confirmed by an external, independent, blinded committee comprised of experienced cardiologists and an oncologist [for potentially cancer-related events]) in Studies 20030216 and 20040138 (Figure 26). Incidences of positively adjudicated events of arrhythmias were balanced between treatment groups in the treatment of PMO fracture study (20030216) (1.4% denosumab, 1.2% placebo) and in the HALT prostate cancer study (20040138) (3.0% denosumab, 2.4% placebo).

Figure 26. Positively Adjudicated Cardiovascular Serious Adverse Events in the Treatment of PMO Fracture Study (20030216) and the HALT Prostate Cancer Study (20040138) (Risk Ratio and 95% CI)



N = Number of subjects who received ≥ 1 dose of investigational product

n = Number of subjects with ≥ 1 event

Hazard ratios and 95% CI based on the Cox proportional hazards model (stratified by study for the overall results) with treatment group and baseline cardiovascular risk level as the independent variables.

In Study 20030216, semiquantitative analysis of abdominal aortic calcification was undertaken in a high-risk cardiovascular subset of subjects to assess effects on aortic

calcification. No difference between treatment groups was observed in the change from baseline in aortic calcification in the subset of subjects at high cardiovascular risk.

In the Primary PMO Safety Analysis Set (Studies 20030216 and 20040132), the incidence of hypercholesterolemia reported as an adverse event term was greater in subjects who received denosumab (7.0%) than in subjects who received placebo (5.9%). There is no biologic mechanism to explain any possible difference in the incidence of this adverse event. Although serum cholesterol levels were not collected in clinical studies, in a nonclinical model of hypercholesterolemia, long-term RANKL inhibition with OPG had no effect on serum cholesterol levels ([Morony et al, 2008](#)). In addition, there were no changes in serum cholesterol in monkeys dosed for up to 12 months with denosumab at 150 times the clinical exposure.

There is no evidence that denosumab has an indirect or direct impact on QTc interval. Because denosumab has a high affinity ($K_d 3 \times 10^{-12}$ M) and specificity for RANKL and a molecular weight of 150 kD (thereby limiting distribution into the intracellular compartment of cardiac myocytes in vivo), it was not anticipated that denosumab would have a direct effect on potassium channels. In preclinical evaluations, which included a cardiovascular safety pharmacology study in monkeys and a 12-month toxicology study in cynomolgus monkeys with ECG monitoring, denosumab did not prolong the QTc interval by either a direct or indirect effect. In the 17 clinical studies that included ECG evaluations, denosumab administration was not associated with clinically significant ECG abnormalities. No abnormal and clinically significant ECG assessments were noted for subjects who had reductions in albumin-adjusted serum calcium concentrations below the normal range. Taken together, the ECG results gave no evidence to suggest that denosumab is associated with adverse cardiovascular effects.

The assessments included in this comprehensive evaluation of cardiovascular data in clinical trials revealed no evidence of increased cardiovascular risk with denosumab administration.

7.5.8 Malignancy

The incidence of malignancies in the pivotal phase 3 PMO and HALT studies was generally balanced between the treatment group (4.2% denosumab, 3.6% placebo) groups ([Table 30](#)), as were the incidences of fatal adverse events of malignancy (0.5% denosumab, 0.7% placebo).

Table 30. Incidence of Malignancies With Incidence $\geq 0.2\%$ in Either Treatment Group (Primary PMO and HALT Combined Safety Analysis Set)

	PMO ^a		HALT ^{a,b}		Overall	
	Placebo (N=4041) n (%)	Denosumab (N=4050) n (%)	Placebo (N=845) n (%)	Denosumab (N=860) n (%)	Placebo (N=4886) n (%)	Denosumab (N=4910) n (%)
Adverse events of malignancy	136 (3.4)	161 (4.0)	39 (4.6)	44 (5.1)	175 (3.6)	205 (4.2)
Breast cancer	26 (0.6)	34 (0.8)	1 (0.1)	0 (0.0)	27 (0.6)	34 (0.7)
Colon cancer	8 (0.2)	11 (0.3)	4 (0.5)	5 (0.6)	12 (0.2)	16 (0.3)
Lung neoplasm malignant	9 (0.2)	9 (0.2)	2 (0.2)	2 (0.2)	11 (0.2)	11 (0.2)
Squamous cell carcinoma of skin	8 (0.2)	6 (0.1)	3 (0.4)	5 (0.6)	11 (0.2)	11 (0.2)
Pancreatic carcinoma	3 (<0.1)	7 (0.2)	0 (0.0)	3 (0.3)	3 (<0.1)	10 (0.2)
Malignant melanoma	5 (0.1)	4 (<0.1)	5 (0.6)	0 (0.0)	10 (0.2)	4 (<0.1)

Note: Table excludes basal cell carcinoma.

^a Malignancy events identified by a search strategy for the treatment of PMO fracture study (20030216; N = 7808 women), the prevention of PMO study (20040132; N = 332 women), and the HALT breast cancer study (20040135; N = 252 women).

^b Malignancy events identified as new primary malignancies in the HALT prostate cancer study (20040138; N = 1468 men).

Although there were numeric differences for individual cancer terms, these differences suggest random variability in the setting of small numbers of events, eg, higher incidence in the denosumab group for pancreatic carcinoma (10 subjects denosumab, 3 subjects placebo) and higher incidence in the placebo group for malignant melanoma (4 subjects denosumab, 10 subjects placebo) (Table 30). No single event of malignancy was reported with a difference in frequency $\geq 0.2\%$ between treatment arms in the combined data sets.

The collective nonclinical and clinical evidence does not support a cancer-promoting effect for denosumab treatment or RANKL inhibition in either healthy or immune compromised subject populations. Indeed, preclinical findings point to the potential therapeutic application of RANKL inhibition with denosumab and are the basis for an extensive phase 3 program in advanced cancer. Malignancies will continue to be monitored in pharmacovigilance program and in ongoing trials in the advanced cancer program.

7.5.9 Impaired or Delayed Fracture Healing

Fracture repair is a complex morphogenetic process involving osteoblastic and osteoclastic actions. During the fracture healing course, cartilage and woven bone are first formed to stabilize the fracture. Callus formation occurs not by bone remodeling but by endochondral bone formation, and therefore does not require osteoclasts or prior bone resorption. After the callus is initially formed it gradually matures and mineralizes, followed by osteoclastic activity that slowly resorbs excess callus to restore the original shape of the bone. Because of the theoretical concern that use of an antiresorptive agent may lead to delay in fracture healing by decreasing bone remodeling, and because patients with bone loss are at increased risk and incidence of fracture, fracture healing in subjects receiving denosumab was evaluated in the nonclinical and clinical programs.

Results from a nonclinical pharmacology study designed to assess fracture repair in huRANKL knock-in mice that were treated with denosumab (10 mg/kg, twice/week SC) or with the bisphosphonate alendronate (0.1 mg/kg, twice/week, SC) starting 2 days after fracture demonstrated that although alendronate and denosumab delayed the removal of cartilage and remodeling of the fracture callus, the mechanical integrity of fractured bones in mice receiving these treatments was not diminished. In fact, whole bone mechanical properties, such as strength and stiffness, were enhanced in these treatment groups when compared with these properties in control bones.

Results from the clinical program demonstrated no untoward clinical impact on the union and healing of fractures. In the Fracture Healing Complication Analysis Set (ie, Studies 20030216, 20040135, and 20040138; n = 9467), such cases were rare (3 in denosumab-treated subjects and 4 in placebo-treated subjects), and all were complicated fractures that required extended time to repair.

7.6 Safety in Subjects Previously Treated With Bisphosphonates

Two randomized studies (phase 1 Study 20050241 and phase 3 Study 20050234) evaluated the effects of denosumab administration in subjects who transitioned from alendronate to denosumab. Both studies included control groups of subjects who maintained their prestudy alendronate dosing. No unique safety findings were observed, and no further reductions in serum calcium were noted in subjects who transitioned from alendronate to denosumab therapy.

Results from Study 20050234 were consistent with analyses from a larger, integrated, data pool (n = 1845), in which the incidences of adverse events, SAEs, and adverse events leading to treatment withdrawal were similar with denosumab administration relative to alendronate. The safety profile in subjects administered denosumab who transitioned from alendronate therapy was not notably different from that observed in treatment-naïve subjects administered denosumab. Additionally, bone histology was normal following treatment with denosumab in subjects who transitioned from alendronate to denosumab therapy (in 36 samples evaluated as part of a substudy). These results demonstrated that patients who have previously received bisphosphonate therapy could safely transition to receive denosumab.

7.7 Long-term Safety

Extensive data on long-term denosumab exposure (ie, > 1 year) have been evaluated. Studies 20030216, 20040132, 20040135, 20040138, and 20010223/20050233 (parent and extension studies) provide between 2 and 5 years of continuous denosumab exposure. More than 4000 subjects have received at least 3 years of denosumab exposure in clinical studies provided in the marketing application. Three-year comparative data are available from > 3700 subjects who received placebo in these studies. Treatment experience in Study 20010223 and its extension study, 20050233, provides the longest duration of continuous denosumab exposure, encompassing ≥ 5 years in subjects (n = 124) with postmenopausal bone loss.

Long-term results from this safety database indicate no specific, unique, or worsened findings apparent with respect to adverse events (including hypocalcemia, neoplasms, infections, hypersensitivity, cardiovascular events [by system organ class], and ONJ), SAEs, laboratory findings (eg, serum calcium decreases), fracture incidence and repair, or antibody formation to suggest that duration of exposure has any impact on the safety profile with denosumab. The safety profile of denosumab appears stable with extended exposure of up to 5 years in duration.

Long-term treatment with bisphosphonates has been linked to the development of ONJ and of atypical (subtrochanteric femur) fractures. These events have not been observed in denosumab-treated subjects in the PMO and HALT clinical programs. ONJ and fracture adverse events will continue to be followed in ongoing safety extension studies and in spontaneous reports.

Several denosumab studies will provide long-term exposure data. The largest data set in this regard will come from Study 20060289, the open-label extension of Study

20030216, the phase 3 pivotal fracture efficacy trial in women with PMO. In Study 20060289, all subjects will receive denosumab 60 mg SC Q6M for 7 years (for a total of 10 years in subjects who received denosumab in the parent study). A total of 4550 subjects enrolled in Study 20060289, 2343 subjects who are continuing treatment with denosumab (long-term treated subjects) and 2207 subjects who received placebo in the parent study and are receiving denosumab for the first time in the current study (de novo treated subjects). Although these data are uncontrolled, and caution will be necessary in their interpretation, this dataset is among the largest postmarketing, prospective collection of safety data in PMO to date.

8. Pharmacovigilance Program

8.1 Key Points

- The size of the denosumab clinical program provided 80% power to detect a 2-fold increase in background events occurring at a rate of 4/1000 or higher.
- A systematic and comprehensive postmarketing pharmacovigilance program for denosumab is proposed. Risk assessment will include evaluation of ongoing long-term safety studies in PMO and HALT and from the advanced cancer program. More than 8000 patients are currently enrolled with denosumab exposure planned for up to 10 years.
- A randomized, placebo-controlled clinical trial will evaluate the risk of cataracts in men with prostate cancer receiving ADT.
- A postmarketing pharmacoepidemiology observational study using available health systems databases is planned to include approximately 380,000 women with PMO exposed to denosumab for up to 5 years in real world settings. The study is designed to have 80% power to detect a 2-fold increase in risk in the exposed cohort, compared with an unexposed cohort, for events with an incidence rate in the unexposed cohort as low as 2.5/100,000.
- Risks for hypocalcemia and skin infections leading to hospitalization, and potential risk for ONJ, can be appropriately managed through product labeling and continued risk assessment through the pharmacovigilance program.

8.2 Pharmacovigilance

Amgen is proposing a systematic and comprehensive pharmacovigilance program, including both routine and proactive pharmacovigilance activities, to monitor the safety profile of denosumab.

Routine pharmacovigilance activities include the following.

- Assessment of events reported from ongoing clinical trials and spontaneous reports from the postmarketing experience.
- Regular reviews of individual and aggregate adverse event data for potential safety signals.
- Cumulative reporting of events of interest in periodic reports and preparation of periodic safety reports (PSRs) and periodic safety update reports (PSURs) to regulatory agencies.

Proactive pharmacovigilance activities include the following.

- Targeted surveillance and the use of focused questionnaires for specific adverse events of interest that are reported in clinical trials and from the postmarketing experience.

- A postmarketing multinational observational study using large administrative health care databases to further elucidate the risk and incidence of adverse events of interest ([Section 8.4](#)). These databases will enable the detection of rare events occurring with a frequency as low as 2.5/100,000 and facilitate analyses of prespecified adverse events of interest and describe potential off-label use of denosumab in the real world setting.
- Continued monitoring and adjudication of ONJ in ongoing and planned clinical trials.
- A prospective, randomized, placebo-controlled study to further evaluate the incidence of cataracts in men receiving denosumab concurrently with ADT for prostate cancer.
- Amgen will also develop and maintain a prospective, observational pregnancy exposure registry in the United States that contrasts the pregnancy and fetal outcomes of women exposed to denosumab during pregnancy to an unexposed control population.

Amgen has appropriate internal processes for evaluating and communicating new safety concerns and changes to existing safety information. Safety signals are initially evaluated by a global cross-functional safety team and concerns which are identified are escalated to a Product Safety Review Meeting which approves communication of identified safety concerns through changes to the reference safety information and health care provider letters as required.

8.3 Ongoing Risk Assessment

Amgen's continuing development program for denosumab will permit systematic and comprehensive risk assessment from ongoing clinical trials in PMO, HALT, and advanced cancer. In the postmarketing setting, appropriate pharmacovigilance and pharmacoepidemiologic assessments of observational data will permit additional characterization of the risk profile, including long-term risks and the evaluation of risk minimization activities.

Ongoing clinical trials with details of patient exposures are listed below.

- Ongoing, long-term, open-label extensions to the pivotal clinical trials in both PMO and HALT which will characterize the long-term safety profile of the molecule and provide up to 10 years of data. These studies include:

- An open-label, 7-year extension to the treatment of PMO fracture study (20030216) in approximately 4500 subjects (total exposure up to 10 years) (Study 20060289)
- A 4-year extension to the phase 2 dose-ranging study (20010223) in 200 subjects (total exposure up to 8 years) (Study 20050233)
- A 2-year extension to the HALT prostate cancer study (20040138) in approximately 800 subjects (total exposure up to 5 years) (Study 20080537)
- Ongoing, controlled clinical trials in PMO and HALT. These studies include:
 - An additional phase 3, fracture efficacy study in women with breast cancer receiving AIT, conducted by the Austrian Breast & Colorectal Cancer Study Group (ABCSG) cooperative group (N = 2800) (Study 20050209)
 - An ongoing study examining the preference, adherence, and satisfaction patterns for denosumab and bisphosphonates (N = 250) (Study 20060232)
- Other ongoing controlled studies in the advanced cancer indication (briefly described in [Section 3.6](#)):
 - Use of denosumab in patients with advanced cancers (breast, prostate and solid tumors) and with bone metastases (N = 5732) (Studies 20050103, 20050136, and 20050244)
 - Patients with hormone-refractory prostate cancer who are at risk of developing bone metastases (N = 1435) (Study 20050147)

Planned studies in PMO and HALT are listed below.

- A prospective, randomized, placebo-controlled study is planned to evaluate new or worsening lens opacifications in men with nonmetastatic prostate cancer receiving denosumab for bone loss due to ADT (N = 760) (Study 20080560, discussed in [Section 8.4](#))
- Two studies examining the efficacy of denosumab compared to other antiresorptive therapies for PMO (N = 800 planned per study) (Studies 20080099 and 20080562)

Activities in the postmarketing setting are listed below.

- Spontaneous adverse event reports from the postmarketing experience, including literature reports, will be collected through standard channels; however, the query process for specific adverse events of interest will be enhanced by the use of focused questionnaires. Data obtained will be used to evaluate causality, frequency, and potential mechanisms of any newly identified safety concerns. Data will be reported as per regulatory guidelines as individual expedited reports or aggregate periodic reports.
- A postmarketing pharmacoepidemiology observational study using available health systems databases is planned to include approximately 380,000 women with PMO exposed to denosumab for up to 5 years in real world settings ([Section 8.4](#)).
- Although pregnancy is not anticipated in these populations, Amgen will also develop and maintain a prospective, observational pregnancy exposure registry that contrasts the pregnancy and fetal outcomes of women exposed to denosumab during pregnancy to an unexposed control population. This registry aims to detect and record major and minor congenital anomalies, spontaneous abortions, stillbirths, elective terminations, and any serious adverse pregnancy outcomes. These events will be assessed among the enrolled women throughout the pregnancy. Developmental abnormalities of the bones will also be assessed among infants up until the first year of life. Annual interim reports will be submitted.

8.4 Observational Study in PMO

The extensive use of electronic medical records by several large healthcare systems and the access to these data allows for robust assessment of selected safety data and estimation of risks from patients in routine clinical practice receiving the product of interest. The planned Denosumab Post-Marketing Global Safety Assessment (DPMGSA) is an observational cohort study of women with PMO. The overall purpose of the study is to allow Amgen to proactively evaluate and quantify specified adverse events of interest and to detect and evaluate newly detected safety signals in the postmarketing period. Patients (both denosumab-exposed and -unexposed) will be followed for at least 1 year and up to 5 years. Additional details regarding this study are provided in [Appendix 6](#).

The primary data systems under consideration for use in this study include:

- US Medicare
- Kaiser Permanente Medical Care Program (KPMCP)
- United HealthCare
- Nordic (Denmark, Finland, Sweden, Norway) National Health Registries

This study will be conducted in 2 stages: prelaunch and postlaunch. In the prelaunch phase, advantages, the limitations and the feasibility of each selected data system to address study objectives will be assessed. The initial feasibility assessment will allow assignment of specific objectives to each data system based upon ability of that data system to address the specific objectives in a scientifically appropriate and valid manner. The prelaunch phase will address challenges relating to database studies, including validation of outcomes and the control of confounding variables by indication and severity.

In the postlaunch phase, planned assessments include the following:

- Incidence rates of prespecified adverse events of interest and related risk factors in women with PMO exposed to denosumab.
- Comparison of the incidences of prespecified identified and potential risks between denosumab-exposed and non-exposed women with PMO.
- Comparison of the incidences of prespecified adverse events of interest between denosumab-exposed patients and patients treated with other osteoporosis therapies.
- Denosumab utilization patterns, including dosage, frequency, length of utilization and stop/switch rate, in PMO women who receive denosumab therapy.
- Patient characteristics and clinical features of women with PMO treated with denosumab.
- Reliable detection of incidences of rare events.

The exact sample size available for this study is not precisely known, but is estimated to be approximately 380,000 patients exposed to denosumab in the 5 years following the launch of denosumab. Given the expected large sample size, this study should be able to reliably evaluate incidences of rare events, either within each data system or in combined analysis over multiple data systems. The estimated 960,000 patient-years of

follow-up will provide 80% power ($\alpha = 0.05$) to detect a 2-fold increase in risk (RR=2) in the exposed cohort, compared with an unexposed cohort, for events with an incidence rate in the unexposed cohort as low as 2.5/100,000.

Prospective annual analyses will be conducted for each prespecified outcome using the most appropriate study database(s). Annual assessments will be descriptive in nature, with results communicated with appropriate contextualization to regulatory agencies within 60 days or as appropriate. If a significant risk (based on statistical analyses and/or medical opinion) is apparent in an annual assessment, the results will be communicated as appropriate.

8.5 Pharmacovigilance Program

A pharmacovigilance program is proposed that is based on the cumulative safety data obtained from the development program to date. The nature and severity of the risks identified in the denosumab program (described in [Section 6.7](#)) can be appropriately managed through the prescribing information. The risks associated with denosumab use and the relevant risk minimization and management of events will be discussed under the appropriate sections of the proposed prescribing information.

Approved prescribing information describing the conditions in which denosumab can be used safely and effectively will serve as the primary risk minimization approach.

Amgen will continue to monitor the benefit-risk balance of denosumab treatment, and re-evaluate the need for additional risk minimization activities, or updates to the prescribing information, on an ongoing basis. Specifically for the prespecified adverse events of interest, Amgen recognizes that additional safety information obtained from the proposed postmarketing studies will enhance the overall safety evaluation.

Events of interest listed in [Table 31](#) are proposed to be monitored in the clinical trial program as well as in the postmarketing observational studies.

Table 31. Pharmacovigilance Activities and Risk Minimization Activities for Events of Interest

Risk	Pharmacovigilance Activity	Risk Minimization Activities
Hypocalcemia	<p>Routine Surveillance: Assessment of events from ongoing clinical trials and spontaneous reports</p> <p>Proactive Surveillance: Focused questionnaire for targeted follow-up of spontaneous reports of hypocalcemia adverse events Rates of hospitalization for hypocalcemia will be reported from the proposed postmarketing observational study. Cumulative analysis in PSUR and annual reports from this study</p>	<p>Contraindication for use if hypocalcemic</p> <p>Recommended monitoring in patients predisposed to hypocalcemia</p> <p>Calcium and vitamin D supplementation recommended</p>
Skin Infections Leading to Hospitalization	<p>Routine Surveillance: Assessment of events from ongoing clinical trials and spontaneous reports</p> <p>Proactive Surveillance: Focused questionnaire for targeted follow-up of spontaneous reports of SAEs of skin infections to identify risk factors, incidence and clinical outcomes. Rates and evaluation of skin infections leading to hospitalization to elucidate risks, nature and incidence will be reported from the observational database study. Cumulative analysis in PSUR and annual reports from this study</p>	<p>Advise patients to seek prompt medical attention if they develop signs or symptoms of cellulitis</p>

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ADR = adverse drug reaction; ADT = androgen deprivation therapy; CRF = case report form; N/A = not applicable; ONJ = osteonecrosis of the jaw; PSUR = Periodic safety Update Report

Table 31. Pharmacovigilance Activities and Risk Minimization Activities for Events of Interest

Risk	Pharmacovigilance Activity	Risk Minimization Activities
Infections	<p>Routine Surveillance: Assessment of events from ongoing clinical trials and spontaneous reports</p> <p>Proactive Surveillance: Targeted follow-up of postmarketing reports using a focused questionnaire to identify risk factors, incidence and clinical outcomes Rates of infection will be reported from long-term evaluation in the observational database study. Cumulative analysis in PSUR and annual reports from this study</p>	N/A (except as noted above for skin infections leading to hospitalization)
Fracture Healing Complications	<p>Routine Surveillance: Assessment of events from ongoing clinical trials and spontaneous reports.</p> <p>Proactive surveillance: Focused questionnaire for targeted follow-up of spontaneous reports In ongoing study 20050209, information on fracture healing is captured for all fracture adverse events using specific CRF. Rates of delayed healing and non-union will be reported from long-term evaluation in the observational database study. Cumulative analysis in PSUR and annual reports from this study</p>	N/A

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ADR = adverse drug reaction; ADT = androgen deprivation therapy; CRF = case report form; N/A = not applicable; ONJ = osteonecrosis of the jaw;
PSUR = Periodic safety Update Report

Table 31. Pharmacovigilance Activities and Risk Minimization Activities for Events of Interest

Risk	Pharmacovigilance Activity	Risk Minimization Activities
ONJ	<p>Routine Surveillance: Assessment of events from ongoing clinical trials and spontaneous reports.</p> <p>Proactive surveillance: Targeted follow-up of postmarketing reports using a focused questionnaire Continued external, independent adjudication in ongoing clinical trials Rates of ONJ will be reported from long-term evaluation in the observational database study. Cumulative analysis in PSUR and annual reports from this study</p>	Advise patients that good oral hygiene should be practiced during treatment
Hypersensitivity	<p>Routine Surveillance: Assessment of events reported from ongoing clinical trials and spontaneous reports</p> <p>Proactive surveillance: Focused questionnaire to query spontaneous reports of hypersensitivity adverse events Rates of severe hypersensitivity will be reported and characterized from long-term evaluation in the observational database study. Cumulative analysis in PSUR and annual reports from this study</p>	N/A

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ADR = adverse drug reaction; ADT = androgen deprivation therapy; CRF = case report form; N/A = not applicable; ONJ = osteonecrosis of the jaw; PSUR = Periodic safety Update Report

Table 31. Pharmacovigilance Activities and Risk Minimization Activities for Events of Interest

Risk	Pharmacovigilance Activity	Risk Minimization Activities
Immunogenicity	<p>Routine Surveillance: Assessment of loss of efficacy reported from ongoing clinical trials and spontaneous reports</p> <p>Proactive Surveillance: Continued antibody assessment in ongoing clinical trials Amgen will perform antibody assessment upon request for postmarketing cases. Cumulative analysis in PSUR and annual reports from this study</p>	N/A
Cataract in Men With Prostate Cancer Receiving ADT	<p>Routine Surveillance: Assessment of events reported from ongoing clinical trials and spontaneous reports.</p> <p>Proactive Surveillance: Study 20080560, a prospective, randomized, placebo-controlled study, is planned to evaluate new or worsening lens opacifications in men with nonmetastatic prostate cancer receiving denosumab for bone loss due to ADT. The incidence and progression of lens opacifications will be evaluated in approximately 760 subjects using a slit-lamp based evaluation system (Lens Opacities Classification System III [LOCS III]). Assessments will be made every 3 months over a 1-year period. The primary endpoint will be subject incidence of cataract event development or progression by month 12, based on a change of ≥ 1.0 in posterior subcapsular, ≥ 1.0 in cortical, or ≥ 0.7 in nuclear opalescence in the LOCS III score.</p>	N/A

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ADR = adverse drug reaction; ADT = androgen deprivation therapy; CRF = case report form; N/A = not applicable; ONJ = osteonecrosis of the jaw; PSUR = Periodic safety Update Report

Table 31. Pharmacovigilance Activities and Risk Minimization Activities for Events of Interest

Risk	Pharmacovigilance Activity	Risk Minimization Activities
Cardiovascular	<p>Routine Surveillance: Assessment of events reported from ongoing clinical trials and spontaneous reports.</p> <p>Proactive Surveillance: Cumulative analysis in PSUR and annual reports from this study</p>	N/A
Malignancy	<p>Routine Surveillance: Assessment of events reported from ongoing clinical trials and spontaneous reports</p> <p>Proactive Surveillance: Rates of new primary malignancy will be reported from long-term evaluation in the observational database study. Cumulative analysis in PSUR and annual reports from this study</p>	N/A
Potential Off-label Use for Other Indications	<p>Routine Surveillance: Monitoring of off-label use through postmarketing surveillance</p> <p>Proactive Surveillance: Characterization of utilization patterns in the postmarketing observational study</p>	Recommended use only in approved indications

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ADR = adverse drug reaction; ADT = androgen deprivation therapy; CRF = case report form; N/A = not applicable; ONJ = osteonecrosis of the jaw;
PSUR = Periodic safety Update Report

9. Conclusions

9.1 Key Points

- As demonstrated by data from an extensive development program, denosumab, administered SC at a dose of 60 mg Q6M, has a favorable benefit-risk profile in the indications sought:
 - treatment of osteoporosis in postmenopausal women,
 - prevention of osteoporosis in postmenopausal women,
 - treatment and prevention of bone loss associated with hormone ablation therapy with breast cancer, and
 - treatment and prevention of bone loss associated with hormone ablation therapy in patients with prostate cancer.

9.2 Denosumab for the Treatment and Prevention of Postmenopausal Osteoporosis

Osteoporosis is a serious skeletal disorder characterized by compromised bone strength predisposing individuals to an increased risk of fracture ([NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, 2001](#)). The goal of therapy for osteoporosis is to reduce the risk of fracture, since osteoporosis fractures result in clinically significant morbidity, including back pain, disability, and loss of independence ([Cummings and Melton, 2002](#); [Papaioannou et al, 2002](#); [Tosteson et al, 2001](#); [Cree et al, 2000](#)). Mortality rates in the first year after a hip or vertebral fracture are significantly higher than in the general population, and approximately 20% of women die within a year of hip fracture ([Johnell et al, 2004](#); [Leibson et al, 2002](#); [Cooper et al, 1993](#)). It is possible that some of the increase in mortality rate is either a direct or indirect consequence of the fractures.

Despite the availability of therapies for the treatment of osteoporosis, most patients at risk for fractures are either not receiving therapy for osteoporosis or are not receiving therapy for a sufficient duration to benefit from the proven antifracture efficacies of these therapies ([Reginster and Burlet, 2006](#); [Solomon et al, 2005](#)). These observations may be partially due to limitations of currently approved therapies. Consequently, there is a significant unmet need for new treatment options to contribute to the long-term effectiveness of osteoporosis care and effectively reduce the risk of fracture.

Denosumab's unique, targeted mechanism of action (preventing the RANKL–RANK receptor interaction in osteoclasts and osteoclast precursors to block the differentiation, activation, and survival of osteoclasts), which results in substantial reductions in bone

resorption, and the proposed dosing regimen (once every 6 months by SC injection), have the potential to significantly impact the effectiveness of osteoporosis treatment. Denosumab rapidly and significantly reduces bone turnover markers and increases BMD, both in postmenopausal women with osteoporosis and in women with low BMD who are at risk for developing osteoporosis. Consistent with denosumab's antiresorptive effect, bone biopsies from denosumab-treated subjects showed normal bone histology and anticipated decreases in bone remodeling. In addition, evidence suggests that denosumab's antiresorptive effects are greater than those of alendronate, both in postmenopausal women who were treatment-naïve and in postmenopausal women who had received therapy with alendronate for at least 6 months, since reductions in bone turnover markers and increases in BMD were significantly larger in denosumab-treated women than in those treated with alendronate. Observed decreases in bone turnover and increases in BMD as a result of denosumab administration (compared with placebo) translated into reductions in the incidence of vertebral, nonvertebral, hip, and major osteoporotic fractures, highlighting the significant clinical benefit of denosumab therapy on clinical outcomes. Antifracture efficacy was demonstrated across a broad range of subpopulations. Antifracture efficacy was sustained for 3 years with no attenuation, and the effect of denosumab was seen as early as 1 year for vertebral fractures and 2 years for nonvertebral and hip fractures.

The effects of denosumab on bone turnover markers and on BMD were reversible after discontinuation of therapy, demonstrating that the bone remains responsive to signaling during and after therapy with denosumab.

Denosumab was generally well tolerated in women with PMO and in women with low BMD. In this patient population, the incidence of all adverse events, SAEs, and deaths were similar in the denosumab and placebo groups. The denosumab safety profile was consistent over time for treatment periods up to 5 years.

Denosumab administration was associated with mild, transient decreases in serum calcium (ie, median decreases from baseline $\leq 3\%$), which were not clinically significant. A number of theoretical risks of denosumab were assessed during the course of the clinical development program, including malignancies, cardiovascular safety, delayed fracture healing, ONJ, hypersensitivity, and immunogenicity; none of these were confirmed as safety issues for denosumab in the PMO and HALT clinical program. Infections also were identified as a theoretical risk, and in the clinical program to date, the overall incidence of infections and opportunistic infections was balanced between

denosumab- and placebo-treated subjects. Infections remain a theoretical risk because of the imbalances in skin infection leading to hospitalization in Study 20030216. Due to the nature of these cases of skin infections, the overall balanced adverse events of skin infections, and the presence of preexisting risk factors, a causal relationship between denosumab treatment and increased risk of skin infections cannot be excluded or confirmed.

9.3 Denosumab for the Treatment and Prevention of Bone Loss Due to HALT

Whereas AIT lowers estrogen levels in postmenopausal women with breast cancer, ADT lowers both testosterone and estrogen in men with prostate cancer through decreased availability of testosterone for conversion to estrogen. As a consequence of these therapies, a further reduction of the already low levels of bioavailable serum estrogen is observed in both older women and men treated with these antineoplastic regimens ([Khosla et al, 1998](#)), which leads to bone loss and increased risk of fractures. Epidemiological studies in men with prostate cancer undergoing ADT and women receiving adjuvant hormonal treatment for breast cancer demonstrated that these patients are at significant risk of low bone mass and developing fractures in the spine and nonvertebral locations ([Shahinian et al, 2005](#); [Buzdar, 2004](#)). No therapies are currently approved for the treatment of bone loss due to HALT.

In the clinical program, the effects of denosumab were rapid in onset, consistent in magnitude across all subpopulations, and sustained for treatment periods up to 3 years. In women with breast cancer receiving AIT and in men with prostate cancer receiving ADT, the effects of denosumab on BMD were consistent across all skeletal sites and similar in magnitude to those observed in women with PMO and in women with low BMD. Furthermore, in the study of men receiving ADT for prostate cancer (20040138), denosumab resulted in a clinically relevant and statistically significant reduction in new vertebral fractures that was similar in magnitude to that observed in women with PMO (Study 20030216). While BMD is not recognized as a surrogate endpoint for antifracture efficacy a priori, both Studies 20040138 and 20030216 support the association between pharmacodynamic effects (BMD) and clinical benefit (fracture efficacy) for denosumab in populations of subjects with bone loss caused by estrogen deprivation. Effects of denosumab were consistent across demographic subgroups (age, race, and geographic region), as well as across subgroups with varying levels of disease severity (baseline BMD T-score, baseline serum CTX1, and prevalent vertebral fracture). Decreases in bone turnover markers (serum CTX1 and P1NP) support the BMD and fracture efficacy

results. Thus, it is reasonable to extrapolate the fracture efficacy of denosumab in women with PMO and in men with prostate cancer receiving ADT to other patient populations with bone loss resultant from a similar etiology, including those with breast cancer, when the same dosing schedule is used (60 mg SC Q6M). These results indicate that denosumab has the potential to improve treatment and prevention of bone loss associated with HALT in women with breast cancer and men with prostate cancer.

Denosumab was generally well tolerated in men and women receiving HALT. In this patient population, the incidence of all adverse events, SAEs, and deaths were similar in the denosumab and placebo groups. Safety results in the hormone ablation setting were consistent with the safety results in the PMO setting with the exception that cataracts were reported with greater incidence in men with prostate cancer receiving ADT (Study 20040138).

9.4 Overall Benefit and Risk Conclusions

Denosumab has a novel and targeted mechanism of action inhibiting RANKL to prevent osteoclast formation, function, and survival. Reduction in osteoclast function was reflected clinically by consistent rapid reductions in bone turnover markers, increase in BMD and significant fracture risk reduction. Denosumab is not sequestered in the bone, and the effects of denosumab on BMD were reversible upon discontinuation of therapy. Reductions in fracture risk and increases in bone density were consistently observed across skeletal sites. Denosumab may offer an important option for the treatment of postmenopausal osteoporosis and the treatment of bone loss associated with HALT.

In women with PMO, denosumab statistically significantly reduced the risk (compared with placebo) of new vertebral fractures by 68%, nonvertebral fractures by 20%, and hip fractures by 40%. Similarly, in men with prostate cancer receiving ADT, denosumab reduced the risk of vertebral fracture by 62%. In both populations, significant reductions in new vertebral fractures were observed at 1 year and were sustained for 3 years.

The overall safety profile was favorable, based on assessments of 7848 subjects exposed to denosumab. Denosumab administration was associated with mild, transient decreases in serum calcium within the normal range that had no apparent clinical significance. Unexpected safety findings associated with denosumab in the clinical program included skin infections resulting in hospitalization in women with PMO and cataracts in men receiving ADT.

In conclusion, denosumab, administered SC at a dose of 60 mg every 6 months, has a favorable benefit-risk profile for the treatment and prevention of postmenopausal osteoporosis and for the treatment and prevention of bone loss associated with hormone ablation therapy. The overall safety and efficacy of denosumab offer a meaningful alternative to existing therapies, with a dose administration schedule that may contribute to adherence.

10. References

10.1 Literature References

American Cancer Society. How many men get prostate cancer?

http://www.cancer.org/docroot/CRI/content/CRI_2_2_1X_How_many_men_get_prostate_cancer_36.asp?sitearea. Accessed 30 May 2009b.

American Cancer Society. How many women get breast cancer?

http://www.cancer.org/docroot/CRI/content/CRI_2_2_1X_How_many_people_get_breast_cancer_5.asp?sitearea. Accessed 30 May 2009a.

Anderson DM, Maraskovsky E, Billingsley WL, et al. A homologue of the TNF receptor and its ligand enhance T-cell growth and dendritic-cell function. *Nature*. 1997;390:175-179.

Ascott-Evans BH, Guanabens N, Kivinen S. Alendronate prevents loss of bone density associated with discontinuation of hormone replacement therapy: a randomized controlled trial. *Arch Intern Med*. 2003;163:789-794.

ATAC Trialists' Group. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet*. 2005;365:60-62.

Banks E, Beral V, Reeves G, Balkwill A, Barnes I, Million Women Study Collaborators. Fracture incidence in relation to the pattern of use of hormone therapy in postmenopausal women. *JAMA*. 2004;291:2212-2220.

Barrett-Connor E, Wehren LE, Siris ES, et al. Recency and duration of postmenopausal hormone therapy: effects on bone mineral density and fracture risk in the National Osteoporosis Risk Assessment (NORA) study. *Menopause*. 2003;10:412-419.

Baum M, Buzdar A, Cuzick J, et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer: results of the ATAC (arimidex, tamoxifen alone or in combination) trial efficacy and safety update analyses. *Cancer*. 2003;98:1802-1810.

Bekker PJ, Holloway D, Nakanishi A, Arrighi M, Leese PT, Dunstan CR. The effect of a single dose of osteoprotegerin in postmenopausal women. *J Bone Miner Res*. 2001;16:348-360.

Bekker PJ, Holloway DL, Rasmussen AS, et al. A single-dose placebo-controlled study of denosumab (AMG 162), a fully human monoclonal antibody to RANKL, in postmenopausal women. *J Bone Miner Res*. 2004;19:1059-1066.

Bennett BJ, Scatena M, Kirk EA, et al. Osteoprotegerin inactivation accelerates advanced atherosclerotic lesion progression and calcification in older ApoE^{-/-} mice. *Arterioscler Thromb Vasc Biol*. 2006;26:2117-2124.

Black DM, Schwartz AV, Ensrud KE. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. *JAMA*. 2006;296:2927-2938.

Body JJ, Bergmann P, Boonen S, et al. Management of cancer treatment-induced bone loss in early breast and prostate cancer - a consensus paper of the Belgian Bone Club. *Osteoporos Int*. 2007;18:1439-1450.

Body JJ, Facon T, Coleman RE, et al. A study of the biological receptor activator of nuclear factor- κ B ligand inhibitor, denosumab, in patients with multiple myeloma or bone metastases from breast cancer. *Clin Can Res*. 2006;12:1221-1228.

Bolla M, Collette L, Blank L, et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial. *Lancet*. 2002;360:103-106.

Bolla M, Gonzalez D, Warde P, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. *N Engl J Med*. 1997;337:295-300.

Bone HG, Bolognese MA, Yuen CK, et al. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women. *J Clin Endocrinol Metab*. 2008;93:2149-2157.

Boyle WJ, Simonet WS, Lacey DL. Osteoclast differentiation and activation. *Nature*. 2003;423:337-342.

Brown JP, Prince RL, Deal C, et al. Comparison of the effect of denosumab and alendronate on bone mineral density and biochemical markers of bone turnover in postmenopausal women with low bone mass: a randomized, blinded, phase 3 trial. *J Bone Miner Res*. 2009;24:153-161.

Browner WS, Lui L-Y, Cummings SR. Associations of serum osteoprotegerin levels with diabetes, stroke, bone density, fractures, and mortality in elderly women. *J Clin Endocrinol Metab*. 2001;86:631-637.

Brufsky A, Bundred N, Coleman R, et al. Integrated analysis of zoledronic acid for prevention of aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole. *Oncologist*. 2008;13:503-514.

Brufsky A, Harker WG, Beck JT, et al. Zoledronic acid inhibits adjuvant letrozole-induced bone loss in postmenopausal women with early breast cancer. *J Clin Oncol*. 2007;25:829-836.

Bucay N, Sarosi I, Dunstan CR, et al. Osteoprotegerin-deficient mice develop early onset osteoporosis and arterial calcification. *Genes Dev*. 1998;12:1260-1268.

Bundred NJ, Campbell ID, Davidson N, et al. Effective inhibition of aromatase inhibitor-associated bone loss by zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole. ZO-FAST study results. *Cancer*. 2008;112:1001-1010.

Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. *J Bone Miner Res*. 2007;22:465-475.

Burgess TL, Qian Y, Kaufman S, et al. The ligand for osteoprotegerin (OPGL) directly activates mature osteoclasts. *J Cell Biol*. 1999;145:527-538.

Buzdar AU. The ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial: an update. *Clin Breast Cancer*. 2004;5(suppl 1):S6-S12.

Campion JM, Maricic MJ. Osteoporosis in men. *Am Fam Physician*. 2003;67:1521-1526.

Coates AS, Keshaviah A, Thürlimann B, et al. Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1-98. *J Clin Oncol*. 2007;25:486-492.

Cooper C, Atkinson EJ, Jacobsen SJ, O'Fallon WM, Melton LJ 3rd. Population-based study of survival after osteoporotic fractures. *Am J Epidemiol*. 1993;137:1001-1005.

Cree M, Soskolne CL, Belseck E, et al. Mortality and institutionalization following hip fracture. *J Am Geriatr Soc*. 2000;48:283-288.

Cree MW, Juby AG, Carriere KC. Mortality and morbidity associated with osteoporosis drug treatment following hip fracture. *Osteopor Int*. 2003;14:722-727.

Cummings SR, Cawthon PM, Ensrud KE, et al. BMD and risk of hip and nonvertebral fractures in older men: a prospective study and comparison with older women. *J Bone Miner Res*. 2006;21:1550-1556.

Cummings SR, McClung MR, Christiansen C, et al. A phase III study of the effects of denosumab on vertebral, nonvertebral, and hip fracture in women with osteoporosis: results from the FREEDOM trial. *J Bone Miner Res*. 2008;23(Suppl 1):S80. Abstract 1286.

Cummings SR, Melton LJ III. Epidemiology and outcomes of osteoporotic fractures. *Lancet*. 2002;359:1761-1767.

Daniell HW. Osteoporosis after orchiectomy for prostate cancer. *J Urol*. 1997;157:439-444.

Dawson-Hughes B, National Osteoporosis Foundation Guide Committee. A revised clinician's guide to the prevention and treatment of osteoporosis. *J Clin Endocrinol Metab*. 2008;93:2463-2465.

Dennison E, Mohamed MA, Cooper C. Epidemiology of osteoporosis. *Rheum Dis Clin N Am*. 2006;32:617-629.

Dombernowsky P, Smith I, Falkson G, et al. Letrozole, a new oral aromatase inhibitor for advanced breast cancer: double-blind randomized trial showing a dose effect and improved efficacy and tolerability compared with megestrol acetate. *J Clin Oncol*. 1998;16:453-461.

Dougall WC, Glaccum M, Charrier K, et al. RANK is essential for osteoclast and lymph node development. *Genes Dev*. 1999;13:2412-2424.

Eghbali-Fatourehchi G, Khosla S, Sanyal A, Boyle WJ, Lacey DL, Riggs BL. Role of RANK ligand in mediating increased bone resorption in early postmenopausal women. *J Clin Invest*. 2003;111:1221-1230.

Ellis GK, Bone HG, Chlebowski R, et al. Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for non-metastatic breast cancer. *J Clin Oncol*. 2008;26:4875-4882.

Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. *JAMA*. 1999;282:637-645.

Ettinger B, Grady D. The waning effect of postmenopausal estrogen therapy on osteoporosis. *N Engl J Med*. 1993;329:1192-1193.

Falahati-Nini A, Riggs BL, Atkinson EJ, et al. Relative contributions of testosterone and estrogen in regulating bone resorption and formation in normal elderly men. *J Clin Invest*. 2000;106:1553-1560.

Felson DT, Zhang Y, Hannan MT, Kiel DP, Wilson PW, Anderson JJ. The effect of postmenopausal estrogen therapy on bone density in elderly women. *N Engl J Med*. 1993;329:1141-1146.

Gallagher JC, Rapuri PB, Haynatzki G, Detter JR. Effect of discontinuation of estrogen, calcitriol, and the combination of both on bone density and bone markers. *J Clin Endocrinol Metab.* 2002;87:4914-4923.

Genant HK, Engelke K, Prevrhal S. Advanced CT bone imaging in osteoporosis. *Rheumatology (Oxford).* 2008;47(suppl 4):iv9-iv16.

Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. *J Bone Miner Res.* 1993;8:1137-1148.

Goss PE, Ingle JN, Martino S, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *N Engl J Med.* 2003;349:1793-1802.

Greendale GA, Espeland M, Slone S, Marcus R, Barrett-Connor E, PEPI Safety Follow-Up Study (PSFS) Investigators. Bone mass response to discontinuation of long-term hormone replacement therapy: results from the Postmenopausal Estrogen/Progestin Interventions (PEPI) Safety Follow-up Study. *Arch Intern Med.* 2002;162:665-672.

Greenspan SL, Emkey RD, Bone HG, Weiss SR. Significant differential effects of alendronate, estrogen, or combination therapy on the rate of bone loss after discontinuation of treatment of postmenopausal osteoporosis. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med.* 2002;137:875-883.

Guisse TA. Bone loss and fracture risk associated with cancer therapy. *Oncologist.* 2006;11:1121-1131.

Hansen T, Kirkpatrick CJ, Walter C, Kunkel M. Increased numbers of osteoclasts expressing cysteine proteinase cathepsin K in patients with infected osteoradionecrosis and bisphosphonate-associated osteonecrosis—a paradoxical observation? *Virchows Arch.* 2006;449:448-454.

Heiss G, Wallace R, Anderson GL, et al. Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. *JAMA.* 2008;299:1036-1045.

Hillner BE, Ingle JN, Chlebowski RT, et al. American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. *J Clin Oncol.* 2003;21:4042-4057.

Hirbe A, Morgan EA, Uluçkan O, Weilbaeher K. Skeletal complications of breast cancer therapies. *Clin Cancer Res.* 2006;12(20 pt 2):6309s-6314s.

Hofbauer LC, Schoppet M. Clinical implications of the osteoprotegerin/RANKL/RANK system for bone and vascular diseases. *JAMA.* 2004;292:490-495.

Hsu HL, 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.

Johnell O, Kanis J, Odén A, et al. Mortality after osteoporotic fractures. *Osteoporos Int.* 2004;15:38-42.

Johnell O, Kanis JA, Oden A, et al. Predictive value of bone mineral density for hip and other fractures. *J Bone Miner Res.* 2005;20:1185-1194.

Kamel HK, Hussain MS, Tariq S, et al. Failure to diagnose and treat osteoporosis in elderly patients hospitalized with hip fracture. *Am J Med.* 2000;109(4):326-328.

Kanis JA, Borgstrom F, De Laet C, et al. Assessment of fracture risk. *Osteoporos Int.* 2005;16:581-589.

- Kanis JA, Johnell O, De Laet C, et al. A meta-analysis of previous fracture and subsequent fracture risk. *Bone*. 2004b;35:375-382.
- Kanis JA, Johnell O, Oden A, Dawson A, De Laet C, Jonsson B. Ten year probabilities of osteoporotic fractures according to BMD and diagnostic thresholds. *Osteoporos Int*. 2001;12:989-995.
- Kanis JA, Johnell O, Oden A, et al. The risk and burden of vertebral fractures in Sweden. *Osteoporosis Int*. 2004a;15:20-26.
- Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX™ and the assessment of fracture probability in men and women from the UK. *Osteoporos Int*. 2008;19:385-397.
- Kanis JA. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report. WHO Study Group. *Osteoporos Int*. 1994;4:368-381.
- Kendler DL, Benhamou CL, Brown JP, et al. Effects of denosumab vs alendronate on bone mineral density (BMD), bone turnover markers (BTM), and safety in women previously treated with alendronate. *J Bone Miner Res*. 2008;23(Suppl 1):S473. Abstract M395.
- Kearns AE, Khosla S, Kostenuik P. Receptor activator of nuclear factor κ B ligand and osteoprotegerin regulation of bone remodeling in health and disease. *Endocrin Rev*. 2008;29:155-192.
- Keech CA, Sashegyi A, Barrett-Connor E. Year-by-year analysis of cardiovascular events in the Multiple Outcomes of Raloxifene Evaluation (MORE) trial. *Curr Med Res Opin*. 2005;21:135-140.
- Khosla S, Melton LJ 3rd, Atkinson EJ, O'Fallon WM, Klee GG, Riggs BL. Relationship of serum sex steroid levels and bone turnover markers with bone mineral density in men and women: a key role for bioavailable estrogen. *J Clin Endocrinol Metab*. 1998;83:2266-2274.
- Khosla S, Burr D, Cauley J, et al. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res*. 2007;22:1479-1491.
- Kong Y, Feige U, Sarosi I, et al. Activated T cells regulate bone loss and joint destruction in adjuvant arthritis through osteoprotegerin ligand. *Nature*. 1999b;402:304-309.
- Kong YY, Yoshida H, Sarosi I, et al. OPGL is a key regulator of osteoclastogenesis, lymphocyte development and lymph-node organogenesis. *Nature*. 1999a;397:315-323.
- Kostenuik PJ. Osteoprotegerin and RANKL regulate bone resorption, density, geometry, and strength. *Curr Opin Pharmacol*. 2005;5:618-625.
- Kostenuik PJ, Nguyen HQ, McCabe J, et al. Denosumab, a fully human monoclonal antibody to RANKL, inhibits bone resorption and increases BMD in knock-in mice that express chimeric (murine/human) RANKL. *J Bone Miner Res*. 2009;24:182-195.
- Krupski TL, Foley KA, Baser O, Long S, Macarios D, Litwin MS. Health care cost associated with prostate cancer, androgen deprivation therapy and bone complications. *J Urol*. 2007;178:1423-1428.

- Kudlacek S, Schneider B, Woloszczuk W, Pietschmann P, Willvonseder R, Austrian Study Group on Normative Values of Bone Metabolism. Serum levels of osteoprotegerin increase with age in a healthy adult population. *Bone*. 2003;32:681-686.
- Lake DE, Hudis C. Aromatase inhibitors in breast cancer: an update. *Cancer Control*. 2002;9:490-498.
- Lacey DL, Timms E, Tan HL, et al. Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. *Cell*. 1998;93:165-176.
- Leder BZ, LeBlanc KM, Schoenfeld DA, Eastell R, Finkelstein JS. Differential effects of androgens and estrogens on bone turnover in normal men. *J Clin Endocrinol Metab*. 2003;88:204-320.
- Leibson CL, Tosteson AN, Gabriel SE, Ransom JE, Melton LJ. Mortality, disability, and nursing home use for persons with and without hip fracture: a population-based study. *J Am Geriatr Soc*. 2002;50:1644-1650.
- Li X, Ominsky MS, Stolina M, et al. Increased RANK ligand in bone marrow of orchiectomized rats and prevention of their bone loss by the RANK Ligand inhibitor osteoprotegerin. *Bone*. 2009; doi:10.1016/j.bone.2009.06.011. In Press.
- Lindsay R, Scheele WH, Neer R, et al. Sustained vertebral fracture risk reduction after withdrawal of teriparatide in postmenopausal women with osteoporosis. *Arch Intern Med*. 2004;164:2024-2030.
- Lipton A, Steger GG, Figueroa J, et al. Randomized active-controlled phase II study of denosumab efficacy and safety in patients with breast cancer-related bone metastases. *J Clin Oncol*. 2007;25:4431-4437.
- Looker AC, Orwoll ES, Johnston CC Jr, et al. Prevalence of low femoral bone density in older US adults from NHANES III. *J Bone Miner Res*. 1997;12:1761-1768.
- Loser K, Mehling A, Loeser S, et al. Epidermal RANKL controls regulatory T-cell numbers via activation of dendritic cells. *Nat Med*. 2006;12:1372-1379.
- Magaziner J, Lydick E, Hawkes W, et al. Excess mortality attributable to hip fracture in white women aged 70 years and older. *Am J Publ Health*. 1997;87:1630-1636.
- Martino S, Cauley JA, Barrett-Connor E, et al. Continuing outcomes relevant to Evista: breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. *J Natl Cancer Inst*. 2004;96:1751-1761.
- Marx RE, Cillo JE, Ulloa JJ. Oral bisphosphonate-induced osteonecrosis: risk factors, prediction of risk using serum CTX testing, prevention, and treatment. *J Oral Maxillofac Surg*. 2007;65:2397-2410.
- Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg*. 2003;61:1115-1118.
- Mascelli MA, Zhou H, Sweet R, et al. Molecular, biologic, and pharmacokinetic properties of monoclonal antibodies: impact of these parameters on early clinical development. *J Clin Pharmacol*. 2007;47:553-565.
- McClung MR, Lewiecki EM, Cohen SB, et al. Denosumab in postmenopausal women with low bone mineral density. *New Engl J Med*. 2006;354:821-831.
- McCombs JS, Thiebaud P, McLaughlin-Miley C, Shi J. Compliance with drug therapies for the treatment and prevention of osteoporosis. *Maturitas*. 2004;48:271-287.

Medical Research Council Prostate Cancer Working Party Investigators Group. Immediate versus deferred treatment for advanced prostatic cancer: initial results of the Medical Research Council Trial. *Br J Urol*. 1997;79:235-246

Melton LJ 3rd, Alothman KI, Khosla S, Achenbach SJ, Oberg AL, Zincke H. Fracture risk following bilateral orchiectomy. *J Urol*. 2003;169:1747-1750.

Messing EM, Manola J, Sarosdy M, Wilding G, Crawford ED, Trump D. Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer. *N Engl J Med*. 1999;341:1781-1788.

Miller PD. Bisphosphonates: pharmacology and use in the treatment of osteoporosis. In: Marcus R, Feldman D, Nelson DA, Rosen CJ, eds. *Osteoporosis*. 3rd ed. San Diego: Elsevier Academic Press; 2008;1725-1742.

Miller PD, Bolognese MA, Lewiecki EM, et al. Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy: a randomized blinded phase 2 clinical trial. *Bone*. 2008;43:222-229.

Miller RE, Branstetter D, Armstrong A, Kennedy B, Jones J, Cowan L, et al. Receptor activator of NF- κ B ligand inhibition suppresses bone resorption and hypercalcemia but does not affect host immune response to influenza infection. *J Immunol*. 2007;179:266-274.

Min H, Morony S, Sarosi I, et al. Osteoprotegerin reverses osteoporosis by inhibiting endosteal osteoclasts and prevents vascular calcification by blocking a process resembling osteoclastogenesis. *J Exp Med*. 2000;192:463-474.

Morony S, Tintut Y, Zhang Z, et al. Osteoprotegerin inhibits vascular calcification without affecting atherosclerosis in *ldlr*(-/-) mice. *Circulation*. 2008;117:411-420.

Mouridsen H, Gershanovich M, Sun Y, et al. Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. *J Clin Oncol*. 2003;21:2101-2109.

Nabholtz JM, Buzdar A, Pollak M et al. Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. Arimidex Study Group. *J Clin Oncol*. 2000;18:3758-3767.

National Cancer Institute 2000-2005 SEER cancer incidence rates (Caucasian Only) for malignant cancers [Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 17 Regs Public-Use, Nov 2005 Sub (2000-2005)- Linked To County Attributes - Total U.S., 1969-2003 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2006, based on the November 2005 submission].

National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology – prostate cancer, version 1.2008. http://www.nccn.org/professionals/physician_gls/PDF/prostate.pdf. Accessed 09 September 2008.

National Eye Institute, US National Institutes of Health. Prevalence of blindness data tables. http://www.nei.nih.gov/eyedata/pbd_tables.asp. Last modified October 2008. Accessed 24 June 2009.

National Osteoporosis Foundation. Washington, DC. 2008.
<http://www.nof.org/osteoporosis/diseasefacts.htm>. Accessed 29 Jul 2008.

Neele SJ, Evertz R, De Valk-De Roo G, Roos JC, Netelenbos JC. Effect of 1 year of discontinuation of raloxifene or estrogen therapy on bone mineral density after 5 years of treatment in healthy postmenopausal women. *Bone*. 2002;30:599-603.

Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med*. 2001;344:1434-1441.

Nevitt MC, Ettinger B, Black DM, et al. The association of radiographically detected vertebral fractures with back pain and function: a prospective study. *Ann Intern Med*. 1998;128:793-800:1998.

Nevitt MC, Thompson DE, Black DM, et al. Effect of alendronate on limited-activity days and bed-disability days caused by back pain in postmenopausal women with existing vertebral fractures. Fracture Intervention Trial Research Group. *Arch Intern Med*. 2000;160:77-85.

NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy. *JAMA*. 2001;285:785-795.

Oefelein MG, Ricchiuti V, Conrad W, Resnick MI. Skeletal fractures negatively correlate with overall survival in men with prostate cancer. *J Urol*. 2002;68:1005-1007.

Ominsky MS, Smith SY, Jolette J, Vlasseros F, Samadfam R, Kostenuik PJ. Further reductions in bone turnover after transition from alendronate to denosumab in ovariectomized cynomolgus monkeys resulted in maintained or improved cortical and trabecular bone mass and bone strength. *Bone*. 2009a;44(Suppl 2):S438-S439. Abstract P483.

Ominsky MS, Stolina M, Li X, et al. One year of transgenic overexpression of osteoprotegerin in rats suppressed bone resorption and increased vertebral bone volume, density and strength. *J Bone Miner Res*. 2009b;in press.

Ominsky MS, Schroeder J, Smith SY, Farrell DJ, Atkinson JE, Kostenuik PJ. Denosumab (AMG 162), a fully human RANKL antibody, improves cortical and cancellous bone mass and bone strength in ovariectomized cynomolgus monkeys. *J Bone Min Res*. 2007;22 (Suppl. 1):Abstract 1082.

Ominsky MS, Li X, Asuncion FJ, et al. RANKL inhibition with osteoprotegerin increases bone strength by improving cortical and trabecular bone architecture in ovariectomized rats. *J Bone Miner Res*. 2008;23:672-682.

Papaioannou A, Watts NB, Kendler DL, Yuen CK, Adachi JD, Ferko N. Diagnosis and management of vertebral fractures in elderly adults. *Am J Med*. 2002;113:220-228.

Price PA, June HH, Buckley JR, Williamson MK. Osteoprotegerin inhibits artery calcification induced by warfarin and by vitamin D. *Arterioscler Thromb Vasc Biol*. 2001;21:1610-1616.

Prince R, Sipos A, Hossain A, et al. Sustained nonvertebral fragility fracture risk reduction after discontinuation of teriparatide treatment. *J Bone Miner Res*. 2005;20:1507-1513.

Rabenda V, Mertens R, Fabri V, et al. Adherence to bisphosphonates therapy and hip fracture risk in osteoporotic women. *Osteoporos Int*. 2008;19:811-818.

- Reginster JY, Burlet N. Osteoporosis: a still increasing prevalence. *Bone*. 2006;38(2 suppl 1):S4-S9.
- Reid DM, Doughty J, Eastell R, et al. Guidance for the management of breast cancer treatment-induced bone loss: A consensus position statement from a UK Expert Group. *Cancer Treat Rev*. 2008;34:S3-S18.
- Reid IR. Osteonecrosis of the jaw – who gets it, and why? *Bone*. 2009;44:4-10.
- Roopenian DC, Akilesh S. FcRn: the neonatal Fc receptor comes of age. *Nature Rev*. 2007;7:715-725.
- Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. *J Oral Maxillofac Surg*. 2004;62:527-534.
- Russell RGG, Watts NB, Ebetino FH, Rogers MJ. Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. *Osteoporos Int*. 2008;18:733-759.
- Saad F, Adachi JD, Brown JP, et al. Cancer treatment-induced bone loss in breast and prostate cancer. *J Clin Oncol*. 2008;26:5465-5476.
- Shahinian VB, Kuo YF, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. *N Engl J Med*. 2005;352:154-164.
- Simonelli C, Chen Y, Morancey J, et al. Evaluation and management of osteoporosis following hospitalization for low-impact fracture. *J Gen Intern Med*. 2003;18(1):17-22.
- 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.
- Siris ES, Harris ST, Rosen CJ, et al. Adherence to bisphosphonate therapy and fracture rates in osteoporotic women: relationship to vertebral and nonvertebral fractures from 2 us claims databases. *Mayo Clin Proc*. 2006;81:1013-1022.
- Smith MR, Egerdie B, Hernández Toriz N, et al. A randomized, double-blind, placebo-controlled trial of denosumab in men receiving androgen deprivation therapy for non-metastatic prostate cancer. *Eur Urol Suppl*. 2009;8:332. Abstract 846.
- Smith MR, Lee WC, Brandman J, Wang Q, Botteman M, Pashos CL. Gonadotropin-releasing hormone agonists and fracture risk: a claims-based cohort study of men with nonmetastatic prostate cancer. *J Clin Oncol*. 2005;23:7897-7903.
- Smith MR, McGovern FJ, Zietman AL, et al. Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. *N Engl J Med*. 2001;345:948-955.
- Smith MR. Osteoporosis in men with prostate cancer: now for the fracture data. *J Clin Oncol*. 2008;26:4371-4372.
- Solomon DH, Finkelstein JS, Katz JN, et al. Underuse of osteoporosis medications in elderly patients with fractures. *Am J Med*. 2003;115:398-400.
- Solomon DH, Morris C, Cheng H, et al. Medication use patterns for osteoporosis: an assessment of guidelines, treatment rates, and quality improvement interventions. *Mayo Clin Proc*. 2005;80:194-202.
- Sornay-Rendu E, Garnero P, Munoz F, Duboeuf F, Delmas PD.. Effect of withdrawal of hormone replacement therapy on bone mass and bone turnover: the OFELY study. *Bone*. 2003;33:159-166.

Stoch SA, Parker RA, Chen L, et al. Bone loss in men with prostate cancer treated with gonadotropin-releasing hormone agonists. *J Clin Endocrinol Metab.* 2001;86:2787-2791.

Stolina M, Dwyer D, Ominsky MS, Corbin T, Van G, Bolon B, 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.

Stolina M, Guo J, Faggioni R, Brown H, Senaldi G. Regulatory effects of osteoprotegerin on cellular and humoral immune responses. *Clin Immunol.* 2003;109:347-354.

Stolina M, Ominsky MS, Schroeder J, Atkinson JE, Smith SY, LeSateur L, et al. Long-term denosumab administration had no observed effects on WBC counts, immune parameters, or T-cell-dependent immune response in non-human primates. *Calcif Tissue Int.* 2008;82(Suppl. 1):S248. (abstract)

Thijssen JH, Blankenstein MA. Endogenous oestrogens and androgens in normal and malignant endometrial and mammary tissues. *Eur J Cancer Clin Oncol.* 1989;25:1953-1959.

Thomsen K, Riis BJ, Johansen JS, Christiansen C, Rodbro P. Bone turnover in postmenopausal women after withdrawal of estrogen/gestagen replacement therapy. *Gynecol Endocrinol.* 1987;1:169-175.

Tosteson AN, Gabriel SE, Grove MR, Moncur MM, Kneeland TS, Melton LJ, III. Impact of hip and vertebral fractures on quality-adjusted life years. *Osteoporos Int.* 2001;12:1042-1049.

Tremollieres FA, Pouilles JM, Ribot C. Withdrawal of hormone replacement therapy is associated with significant vertebral bone loss in postmenopausal women. *Osteoporos Int.* 2001;12:385-390.

Ueland T, Jemtland R, Godang K, et al. Prognostic value of osteoprotegerin in heart failure after acute myocardial infarction. *J Am Coll Cardiol.* 2004;44:1970-1976.

van den Boogaard CHA, Breekveldt-Postma NS, Borggreve SE, Goettsch WG, Herings RMC. Persistent bisphosphonate use and the risk of osteoporotic fractures in clinical practice: a database analysis study. *Curr Med Res Opin.* 2006;22:1757-1764.

Van den Wyngaert T, Huizing MT, Vermorken JB. Bisphosphonates and osteonecrosis of the jaw: cause and effect or a post hoc fallacy? *Ann Oncol.* 2006;17:1197-1204.

Wasnich RD, Bagger YZ, Hosking DJ, et al. Changes in bone density and turnover after alendronate or estrogen withdrawal. *Menopause.* 2004;11:622-630.

Watts NB, Chines A, Olszynski WP, et al. Fracture risk remains reduced one year after discontinuation of risedronate. *Osteoporos Int.* 2008;19:365-372.

Weycker D, Macarios, Edelsberg J, Oster G. Compliance with drug therapy for postmenopausal osteoporosis. *Osteoporos Int.* 2006;17:1645-1652.

Wu M, Goss PE. Update on the use of letrozole in breast cancer. *Expert Opin Pharmacother.* 2007;8:2329-2345.

Yamaguchi T, Sakaguchi S. Skin controls immune regulators. *Nat Med.* 2006;12:1358-1359.

Yasuda H, Shima N, Nakagawa N, et al. Osteoclast differentiation factor is a ligand for osteoprotegerin/osteoclastogenesis-inhibitory factor and is identical to TRANCE/RANKL. *Proc Natl Acad Sci USA*. 1998;95:3597-3602.

Yates J, Barrett-Connor E, Barlas S, Chen YT, Miller PD, Siris ES. Rapid loss of hip fracture protection after estrogen cessation: evidence from the National Osteoporosis Risk Assessment. *Obstet Gynecol*. 2004;103:440-446.

Zhou Z, Redaelli A, Johnell O, et al. A retrospective analysis of health care costs for bone fractures in women with early stage breast carcinoma. *Cancer*. 2003;100:507-517.

10.2 Links to Prescribing Information for Approved Therapies

Actonel® (risedronate sodium) Tablets Prescribing Information. Procter and Gamble. Accessed 18 June 2009 at: http://www.actonel.com/global/prescribing_information.pdf

Arimidex® (anastrozole) Tablet for Oral Use Prescribing Information. AstraZeneca Pharmaceuticals. Accessed 19 June 2009 at: <http://www1.astrazeneca-us.com/pi/arimidex.pdf>

Aromasin® (exemestane) Tablets Prescribing Information. Pfizer. Accessed 19 June 2009 at: http://www.pfizer.com/files/products/uspi_aromasin.pdf

Boniva® (ibandronate sodium) Tablets Prescribing Information. Roche Pharmaceuticals. Accessed 18 June 2009 at: <http://www.rocheusa.com/products/Boniva/PI.pdf>

Boniva® (ibandronate sodium) Injection Prescribing Information. Roche Pharmaceuticals. Accessed 18 June 2009 at: http://www.rocheusa.com/products/Boniva/Injection_PI.pdf

Evista® (raloxifene hydrochloride) Tablet for Oral Use Prescribing Information. Eli Lilly. Accessed 18 June 2009 at: <http://pi.lilly.com/us/evista-pi.pdf>

Femara® (letrozole) Tablets Prescribing Information. Novartis. Accessed 19 June 2009 at: <http://www.pharma.us.novartis.com/product/pi/pdf/Femara.pdf>

Forteo® (teriparatide [rDNA origin]) Injection Prescribing Information. Eli Lilly. Accessed 18 June 2009 at: <http://pi.lilly.com/us/forteo-pi.pdf>

Fosamax® (alendronate sodium) Tablets and Oral Solution Prescribing Information. Merck. Accessed 18 June 2009 at: http://www.merck.com/product/usa/pi_circulars/f/fosamax/fosamax_pi.pdf

Lupron Depot® (leuprolide acetate for depot suspension) Prescribing Information. Abbott Laboratories. Accessed 19 June 2009 at: http://rxabbott.com/pdf/lupron3month22_5mg.pdf

Premarin® (conjugated estrogens tablets, USP) Prescribing Information. Wyeth Pharmaceuticals. Accessed 18 June 2009 at: <http://www.wyeth.com/content/showlabeling.asp?id=131>

Prempro® (conjugated estrogens/medroxyprogesterone acetate tablets) Prescribing Information. Wyeth Pharmaceuticals. Accessed 18 June 2009 at: <http://www.wyeth.com/content/showlabeling.asp?id=133>

Reclast® (zoledronic acid) Injection Prescribing Information. Novartis. Accessed 18 June 2009 at: <http://www.pharma.us.novartis.com/product/pi/pdf/reclast.pdf>

Xolair® (omalizumab) Prescribing Information. Genentech. Accessed 18 June 2009 at: <http://www.gene.com/gene/products/information/pdf/xolair-prescribing.pdf>

Zoladex® (goserelin acetate implant) Prescribing Information. AstraZeneca Pharmaceuticals. Accessed 19 June 2009 at: http://www1.astrazeneca-us.com/pi/zoladex3_6.pdf

Appendix 1. Approved Therapies for PMO

Chemical Class		Relative Risk Reduction ^a			Mean Lumbar Spine BMD Increase ^a	Key Adverse Events
Therapy (Brand Name)	Dose Regimen(s)	Vertebral	Non-vertebral	Hip		
<u>Antiresorptives</u>						
<i>Bisphosphonates</i>						
Alendronate (Fosamax ^{® b})	10 mg QD PO 70 mg QW PO	47%	None	51%	~7% - 10%	Irritation of upper gastrointestinal mucosa Musculoskeletal pain ONJ
Ibandronate (Boniva [®])	2.5 mg QD PO 150 mg QM PO 3 mg Q3M IV	52%	None	None	5%	The most common adverse reactions (> 5%) are back pain, dyspepsia, pain in extremity, diarrhea, headache, and myalgia. ONJ
Risedronate (Actonel [®])	5 mg QD PO 35 mg QW PO 75 mg X 2 QM PO (taken on 2 consecutive days of the month) 150 mg QM PO	41% - 49%	35% -39%	NR	5.0% - 6.6%	The most common adverse reactions reported in > 10% of patients and with a higher frequency than placebo are: back pain, arthralgia, abdominal pain, and dyspepsia. Hypersensitivity reactions (angioedema, generalized rash, bullous skin reactions), and eye inflammation (iritis, uveitis) have been reported rarely. ONJ

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Efficacy, safety, and dose regimen data are per current US Prescribing Information.

NR = not reported

^a As compared with placebo over 3 years of treatment, except: estrogen and estrogen/ progesterone (24 months for BMD and 6.8 years of follow-up for fracture endpoints) and teriparatide (19 months median exposure)

^b Generic formulations also approved

^c Indicated for prevention, but not treatment, of PMO

Appendix 1. Approved Therapies for PMO

Chemical Class		Relative Risk Reduction ^a			Mean Lumbar Spine BMD Increase ^a	Key Adverse Events
Therapy (Brand Name)	Dose Regimen(s)	Vertebral	Non- vertebral	Hip		
Zoledronic acid (Reclast [®])	5 mg yearly IV	70%	25%	41%	6.7%	The most common adverse reactions (>10%) were pyrexia, myalgia, headache, arthralgia, pain in extremity. Other clinically important adverse reactions were flu-like illness, nausea, vomiting and diarrhea. ONJ
<i>Estrogen receptor agonist/antagonist</i>						
Raloxifene (Evista [®])	60 mg QD PO	55%	NR	NR	2.6%	Increased risk of venous thromboembolism and death from stroke (black box warning) Adverse reactions (>2% and more common than with placebo) include: hot flashes, leg cramps, peripheral edema, flu syndrome, arthralgia, sweating.

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Efficacy, safety, and dose regimen data are per current US Prescribing Information.

NR = not reported

^a As compared with placebo over 3 years of treatment, except: estrogen and estrogen/ progesterone (24 months for BMD and 6.8 years of follow-up for fracture endpoints) and teriparatide (19 months median exposure)

^b Generic formulations also approved

^c Indicated for prevention, but not treatment, of PMO

Appendix 1. Approved Therapies for PMO

Chemical Class		Relative Risk Reduction ^a			Mean Lumbar Spine BMD Increase ^a	Key Adverse Events
Therapy (Brand Name)	Dose Regimen(s)	Vertebral	Non-vertebral	Hip		
<i>Estrogen receptor agonist/antagonist</i> (continued)						
Estrogen (Premarin [®])	0.625 QD PO	38%	NR	39%	4.9%	Endometrial cancer Deep vein thrombosis Stroke
Estrogen/ progesterone ^b (Prempro [®])	0.625 mg / 5 mg QD PO	35%	NR	33%	5.7%	Deep vein thrombosis Stroke
<u>Anabolic agents</u>						
<i>PTH analog</i>						
Teriparatide (Forteo [®])	20 µg QD SC	65%	53%	NR	8.6%	Potential, based on nonclinical data, for osteosarcoma (black box warning) Orthostatic hypotension Dizziness Leg cramps

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Efficacy, safety, and dose regimen data are per current US Prescribing Information.

NR = not reported

^a As compared with placebo over 3 years of treatment, except: estrogen and estrogen/ progesterone (24 months for BMD and 6.8 years of follow-up for fracture endpoints) and teriparatide (19 months median exposure)

^b Generic formulations also approved

^c Indicated for prevention, but not treatment, of PMO

Appendix 2. Fracture Definitions

Category	Definition
New Vertebral Fractures	Symptomatic ^a and asymptomatic vertebral fractures, defined as an increase of ≥ 1 grade in any vertebra from T4 to L4 from the previous grade of 0 ^b
New and Worsening Vertebral Fractures	Symptomatic ^a and asymptomatic new vertebral fractures (as defined above) and worsening vertebral fractures as defined by an increase of ≥ 1 grade from the previous grade of ≥ 1 in any vertebra from T4 to L4
Clinical Vertebral Fractures	New vertebral fracture assessed at either a scheduled or unscheduled visit and associated with any signs or symptoms ^a (or both) indicative of a fracture
Multiple New Vertebral Fractures	Symptomatic ^a or asymptomatic new vertebral fractures observed in ≥ 2 vertebrae from T4 to L4.
Nonvertebral Fractures (Osteoporotic)	Fractures ^a of the hip, forearm, clavicle, rib, humerus, pelvis, leg, and foot.
Any Clinical Fracture	Nonvertebral fractures (osteoporotic) and clinical vertebral fractures, as defined above
Any Osteoporotic Fracture	Nonvertebral fractures (osteoporotic) and new vertebral fractures, as defined above
Major Osteoporotic Fracture (per WHO definition)	Nonpathologic hip, forearm, humerus, and clinical vertebral fractures, regardless of trauma severity.
Major Nonvertebral Fracture (per CHMP definition)	Fractures ^a of the pelvis, distal femur, proximal tibia, rib, proximal humerus, forearm, and hip
Hip Fracture	Fractures ^a of the femur neck, femur intertrochanter, and femur subtrochanter fractures

CHMP = Committee for Medicinal Products for Human Use; WHO = World Health Organization

^a Excludes pathologic fractures and fractures associated with high trauma severity. Fractures were considered to be of high trauma severity if the fracture was the result of a fall from higher than the height of a stool, chair, first rung on a ladder or equivalent (> 20 inches) or was the result of severe trauma other than a fall.

^b Grades of vertebral fractures were assessed per the Genant Semiquantitative Scoring Method (Genant et al, 1993):

Grade 0 (normal)

Grade 1 (mild): 20% to 25% reduction in vertebral height (anterior, middle, or posterior)

Grade 2 (moderate): 25% to 40% reduction in height

Grade 3 (severe): $> 40\%$ reduction in height.

Appendix 3. Statistical Considerations

Pre-Specification of Analysis

For each study, statistical analysis plans documenting the analyses for all endpoints were finalized prior to locking the clinical trial database and un-blinding the treatment assignments. These plans were written, finalized and archived according to Amgen's standard operating procedures while blinded to treatment assignment. Data that were considered potentially un-blinding were received and processed by a separate group within Amgen who supplied scrambled data to the study team to ensure the blind was not broken. Analyses were executed per the statistical analysis plans, and any analysis that was not pre-specified in the statistical analysis plan is considered *post hoc* and noted as such in this document.

Intention-to-treat Principle

Amgen designed, conducted and analyzed data following the intention-to-treat principle.

The protocols for all denosumab phase 3 studies specified that subjects were to be followed up regardless of whether or not subjects remained on investigational product or if subjects received alternate therapy during the course of study. Investigators were asked to encourage the subjects to continue to participate in study procedures. As long as a subject did not completely withdraw consent from the study, investigators continued making the protocol specified assessments. All available data was used in the analyses, regardless of compliance to therapy or taking alternate therapies.

Clinical fracture endpoints included all randomized subjects (full analysis set). Subjects who did not experience an event while on study were censored at the last on-study day for both those who completed the study and those who withdrew early. Subjects who had no post-baseline follow-up information were considered censored at study day 1.

Endpoints with reference to baseline such as new vertebral fractures and percent change in BMD required that subjects have a baseline and at least one post baseline evaluation to be included in the analyses. Primary imputation for missing data in these situations was last observation carried forward.

Multiplicity Adjustment

In the protocols and the statistical analysis plans, testing strategies to address multiplicity issues were pre-specified for primary and secondary endpoints. The testing strategies for the pivotal phase 3 studies are presented in the following table.

Statistical Testing Strategies for Pivotal Phase 3 Studies

Study	Method Detail	Steps - Endpoints
20030216 Treatment of PMO Fracture Study	Step-down All endpoints evaluated through month 36. Hierarchical testing procedure where inferential testing is continued at next step only if previous step is significant at the 5% level.	Step 1: - New vertebral fracture Step 2: - Nonvertebral fracture Step 3: - Hip fracture
20040132 Prevention of PMO	Bonferroni/Stepdown/Hochberg All endpoints are percent change at 24 months. BMD measured by DXA except where noted. Testing is performed within each randomization stratum defined by time since menopause (≤ 5 years, > 5 years) at the 2.5% level. Hierarchical testing procedure where inferential testing continues to Step 2 only if Step 1 is significant at the 2.5% level. Multiple endpoints within Step 2 are simultaneously tested using Hochberg's method.	Step 1: - Lumbar spine BMD Step 2: - Total hip BMD - Femoral neck BMD - Trochanter BMD - Distal 1/3 radius BMD - Total body (without head) BMD - Distal radius trabecular BMD (QCT) - Distal radius cortical BMD (QCT) - Distal radius total BMD (QCT)
20040138 HALT Prostate Cancer	Step-down/Hochberg All BMD endpoints are percent change from baseline as measured by DXA. Hierarchical testing procedure where inferential testing continues at next step only if previous step is significant at the 5% level. For steps with multiple endpoints, all endpoints must be significant to continue. Multiple endpoints within a step are simultaneously tested using Hochberg's method.	Step 1: - Lumbar spine BMD (month 24) Step 2: - Femoral neck BMD (month 24) - Total hip BMD (month 24) Step 3: - Lumbar spine BMD (month 36) - Femoral neck BMD (month 36) - Total hip BMD (month 36) Step 4: - Any fracture (morphometric vertebral + clinical fractures) [month 36] - New vertebral fracture (month 36) Step 5: - Clinical fracture (month 36) Step 6: - Any fracture (morphometric vertebral + clinical fractures) [month 24]

Statistical Testing Strategies for Pivotal Phase 3 Studies

Study	Method Detail	Steps - Endpoints
20040135 HALT Breast Cancer	Step-down/Hochberg All BMD endpoints are percent change from baseline as measured by DXA. Hierarchical testing procedure where inferential testing is continued at next step only if previous step is significant at the 5% level. Simultaneously test multiple endpoints within a step using Hochberg's method	Step 1: - Lumbar spine BMD (month 12) Step 2: - Lumbar spine BMD (month 6) - Total hip BMD (month 6) - Total hip BMD (month 12) - Femoral neck BMD (month 6) - Femoral neck BMD (month 12)

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Analysis Methods

ANCOVA models were used for analysis of BMD endpoints. Logistic regression models were used for endpoints that included morphometric fractures such as new vertebral and any fracture endpoints (see [Appendix 2](#) for fracture definitions). Cox proportional hazards models were used for clinical fracture endpoints such as non-vertebral fractures. All models were either adjusted (ANCOVA, logistic regression) for or stratified by the individual study randomization stratification. Score statistics were used for both the logistic regression models and Cox's proportional hazards model.

Sensitivity analyses were pre-specified in the statistical analysis plans for primary and secondary endpoints to assess the validity and robustness of the primary analysis. These sensitivity analyses included using

- per-protocol subsets which excluded subjects who had specific pre-specified major protocol deviations
- different statistical models for analysis
- different imputation techniques

A key sensitivity analysis was using repeated measures mixed models as an alternative method to last observation carried forward imputation for handling missing BMD data.

None of the sensitivity analyses for the primary and key secondary endpoints for the studies presented in this document showed any marked deviations from the primary analyses.

Appendix 4. Hypersensitivity Search Terms

Listed below are MedDRA preferred terms used in the search strategy for hypersensitivity.

Hypersensitivity

(Adverse Events Potentially Associated with Hypersensitivity via Standardized MedDRA Queries [SMQs]; Narrow search/scope of Angioedema, Anaphylactic Reaction, and Severe Cutaneous Adverse Reactions SMQs):

Preferred Term in MedDRA v11.0	
ACUTE GENERALISED EXANTHEMATOUS PUSTULOSIS	ALLERGIC OEDEMA
ANAPHYLACTIC REACTION	ANAPHYLACTIC SHOCK
ANAPHYLACTOID REACTION	ANAPHYLACTOID SHOCK
ANGIOEDEMA	CIRCULATORY COLLAPSE
CIRCUMORAL OEDEMA	CONJUNCTIVAL OEDEMA
CORNEAL OEDEMA	CUTANEOUS VASCULITIS
DERMATITIS BULLOUS	DERMATITIS EXFOLIATIVE
DERMATITIS EXFOLIATIVE GENERALISED	EPIDERMAL NECROSIS
EPIGLOTTIC OEDEMA	ERYTHEMA MULTIFORME
EXFOLIATIVE RASH	EYE OEDEMA
EYE SWELLING	EYELID OEDEMA
FACE OEDEMA	FIRST USE SYNDROME
GINGIVAL OEDEMA	GINGIVAL SWELLING
GLEICH'S SYNDROME	HEREDITARY ANGIOEDEMA
IDIOPATHIC URTICARIA	LARYNGEAL OEDEMA
LARYNGOTRACHEAL OEDEMA	LIP OEDEMA
LIP SWELLING	OCULORESPIRATORY SYNDROME
OEDEMA MOUTH	OROPHARYNGEAL SWELLING
PALATAL OEDEMA	PERIORBITAL OEDEMA
PHARYNGEAL OEDEMA	SCLERAL OEDEMA
SHOCK	SKIN NECROSIS
SMALL BOWEL ANGIOEDEMA	STEVENS-JOHNSON SYNDROME
SWELLING FACE	SWOLLEN TONGUE
TONGUE OEDEMA	TOXIC EPIDERMAL NECROLYSIS
TOXIC SKIN ERUPTION	TRACHEAL OEDEMA
TYPE I HYPERSENSITIVITY	URTICARIA
URTICARIA CHOLINERGIC	URTICARIA CHRONIC
URTICARIA PAPULAR	

Appendix 5. ONJ Search Terms

Listed below are MedDRA preferred terms used in the search strategy for potential events of ONJ.

Preferred Term in MedDRA v11.0	
ABSCESS JAW	ABSCESS ORAL
ALVEOLAR OSTEITIS	BONE DEBRIDEMENT
BONE EROSION	BONE FISTULA
BONE INFARCTION	DENTAL FISTULA
DENTAL NECROSIS	GINGIVAL ABSCESS
GINGIVAL EROSION	GINGIVAL ULCERATION
JAW LESION EXCISION	JAW OPERATION
LOOSE TOOTH	MAXILLOFACIAL OPERATION
NECROSIS	ORAL CAVITY FISTULA
ORAL SURGERY	OROANTRAL FISTULA
OSTEITIS	OSTEOMYELITIS
OSTEOMYELITIS ACUTE	OSTEOMYELITIS CHRONIC
OSTEOMYELITIS DRAINAGE	OSTEONECROSIS
PAIN IN JAW	PERIODONTAL DESTRUCTION
PERIODONTAL INFECTION	PERIODONTAL OPERATION
PRIMARY SEQUESTRUM	SECONDARY SEQUESTRUM
SEQUESTRECTOMY	TERTIARY SEQUESTRUM

Appendix 6. Synopsis of Denosumab Post-Marketing Global Safety Assessment (DPMGSA)

Background: Clinical studies demonstrate that denosumab is well tolerated in patients followed for up to 5 years. However, based on patient observations or theoretical concerns, hypocalcemia, serious infections (including skin infections), fracture healing complications, osteonecrosis of the jaw (ONJ), hypersensitivity and new primary malignancy have been specified as events of interest for denosumab treated PMO patients.

Accordingly, Amgen has developed a proactive pharmacovigilance study of these events of interest. The study employs several large data sources to assess events of interest and also provides a resource to evaluate ad hoc concerns that may arise in the post-approval period.

Objectives: The proposed study will be conducted in two phases. Objectives of the Phase 1 studies are to:

1. Characterize potential denosumab users in PMO populations and likely comparator groups.
2. Establish and test the validity of algorithms for identifying PMO populations, determining PMO severity and ascertaining the occurrence of study events of interest.
3. Describe background incidence rates of study events of interest using validated case ascertainment algorithms among potential denosumab exposed populations and likely comparator groups.

The results from Phase 1 will support the evaluation of events of interest in Phase 2.

Objectives of the Phase 2 studies are to:

1. Describe and compare, after appropriately adjusting for relevant confounding factors, incidence rates of events of interest in denosumab exposed and unexposed PMO women.
2. Describe denosumab utilization patterns (dosage, frequency, length of utilization, stop / switch treatment) in PMO women receiving denosumab therapy.
3. Describe patient characteristics and clinical features of PMO women treated with denosumab.

Hypotheses: These analyses are considered to be hypothesis-generating, rather than confirmatory.

Study Design and Methods: Cohort analyses in 3 US data systems and 4 Nordic countries will be proposed. In Phase 1, data will be analyzed for the period January 2005 until the launch of denosumab (or a 5 year period) in the respective countries. For Phase 2, data will be collected for a 5 year period starting 6 months after launch.

Data Sources: Four types of data sources are under consideration: US Medicare, California Kaiser Permanente Medical Care Program, United Healthcare, and Nordic (Denmark, Finland, Sweden, Norway) National Health Registries. These sources are widely used for pharmacovigilance research and are well suited for our intended purpose as they, in aggregate: are population-based with significant representation of PMO women (Medicare, Nordic registries); include large numbers of subjects allowing both independent and aggregate analysis; enable long term follow-up (Medicare, Nordic registries); and afford access to medical records for case ascertainment and confirmation (Kaiser Permanente, Nordic registries, United Healthcare).

Eligibility Criteria: Eligibility will be limited to post-menopausal women with a diagnosis of osteoporosis. Identification of such women will be based on a validated algorithm developed during Phase 1, which will generally include diagnostic codes indicating PMO in the specific data system, and/or procedures or relevant PMO treatment, in combination with age criteria (eg, 55 years or older). Patients will be excluded if they have a history of cancer prior to their initiation of denosumab or other PMO therapies.

Outcomes: Incidence rates will be calculated for the following events of interest (background rates in Phase 1; rates in denosumab treated and untreated women in Phase 2):

- Serious hypocalcemia measured by a hypocalcemia diagnosis leading to hospitalization or an emergency room visit, and / or receipt of intravenous calcium medication;
- ONJ identified by a predefined algorithm (developed in the denosumab development program and / or Phase 1 study) and confirmed by medical chart review;
- Serious infections that lead to hospitalization, with a focus on skin infections;
- Serious hypersensitivity reactions that lead to hospitalization or an ER visit, such as anaphylaxis;

- Fracture healing complications as measured by diagnosis codes or notation of delayed fracture healing and fracture non-union in non-vertebral fractures and confirmed by medical chart review;
- New primary malignancy.

Study Size: The number of denosumab-exposed patients in the 5-year post-launch period can be estimated as the sum of: (i) 62,500-125,000 women aged 65 years and older within Medicare; (ii) approximately 30,000 within Kaiser; (iii) approximately 50,000 in United HealthCare; and (iv) approximately 240,000 in the Nordic registries. This will provide the capability to evaluate rare events within each data system or in combined analyses. For example, with 960,000 person-years of follow-up accumulated in each of the denosumab exposed and unexposed groups, the study will have 80% power (type 1 error = 0.05) to detect a two-fold increase in risk of events that have an incidence rate of 2.5 per 100,000 person-years or greater among those not exposed to denosumab.

Statistical Considerations: Each data source has specific strengths and limitations. Statistical analyses, therefore, will use methodological approaches that are either uniform (same approaches including case ascertainment, across data systems) or data system-specific (based upon the best data available in each selected data system).

Activities in Phase 1 include the following:

- *Characterization of potential denosumab users in PMO populations.* Descriptive statistics will characterize patient groups. Specific comparisons of characteristics and study outcomes between new (naïve) and current users of a PMO medication, or patients who continue versus switch from a PMO medication, will facilitate identification of likely sources of bias (eg, selection bias) to be addressed in the post-approval pharmacovigilance studies.
- *Construction of valid case and outcome ascertainment algorithms.* Clearly defined and confirmed standardized case definitions will be developed based on data availability in each data system. Algorithm validity will be verified via medical chart review by medical professionals, pre-specifying target levels of positive and negative predictive values.
- *Background incidence rates of events of interest.* Rates of events of interest among PMO women will be estimated by Kaplan-Meier survival curves. Cox regression models using PMO therapy exposure as a time-varying covariate may be used to compare event rates among study cohorts.

In Phase 2, descriptive statistics will characterize patient groups and denosumab utilization patterns. Time-to-event analysis methods such as Cox proportional hazards regression models using denosumab exposure as a time-varying covariate as well as other time-dependent covariates may be used to describe and compare event rates among denosumab exposed and unexposed women, with an estimation of the hazard ratio and associated 95% confidence interval. One might anticipate, based upon results of Phase 1 analyses, that an important methodological issue will be that specific subsets of patients are 'channeled' to denosumab, such that denosumab users, as compared to those on other treatments, may be at higher risk of one or more of the events of interest. Study design and analytic approaches to address potential sources of bias or effect of important confounding factors such as disease severity or duration of previous osteoporosis treatment will be pre-specified in Phase 2 study protocols and statistical analysis plans. For example, one might address channeling bias by comparing patients who switch to denosumab to those switching to other treatments. Data will be assessed annually with findings reported in appropriate context via the PSUR. A final report will be completed within six months following the end of the study (Q2, 2016).

Summary: The proposed study of databases offers Amgen the opportunity to proactively conduct comprehensive post-approval PMO pharmacovigilance studies based on data systems that are well recognized within the pharmacovigilance community. The specific databases were chosen to complement each other and overcome the limitations of single database analyses, while offering the possibility of evaluating the consistency of findings from any one database. These database analyses will promote understanding of denosumab utilization and facilitate understanding of risks associated with denosumab treatment.