EUROPEAN UNION RISK MANAGEMENT PLAN

Prolia® (denosumab 60 mg)

Marketing Authorization Holder:	Amgen Europe B.V. Minervum 7061 4817 ZK Breda, Netherlands
Version:	31.0
Date:	11 January 2023
Supersedes:	Version 30.0, dated 11 May 2022

Risk Management Plan (RMP) version to be assessed as part of this application

RMP version number:	31.0
Data lock point of this RMP:	26 September 2022
Date of final sign-off:	11 January 2023
Rationale for submitting an updated RMP:	To remove completed category 3 Study 20130173 from the pharmacovigilance plan.

Summary of significant changes in this RMP

Part/Module/Annex	Major Change(s)	Version Number and Date
Part II: Safety Specification		
SIII: Clinical Trial Exposure	Updated clinical trial exposure to a data lock point (DLP) of 26 September 2022.	Version 31.0, 11 January 2023
SIV.2: Limitations to Detect Adverse Reactions in Clinical Trial Development Programs	Removed Table 14, Limitations Common to all Clinical Trials, per template.	Version 31.0, 11 January 2023
SIV.3: Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programs	• Updated clinical trial exposure to a DLP of 26 September 2022. • Updated table title per template.	Version 31.0, 11 January 2023
SV: Postauthorization Experience	Updated postauthorization exposure to a DLP of 26 September 2022.	Version 31.0, 11 January 2023
SVII: Identified and Potential Risks	Updated subject incidence data for the important identified risks of osteonecrosis of the jaw and hypercalcemia in pediatric patients receiving denosumab and after treatment discontinuation.	Version 31.0, 11 January 2023
PART III: Pharmacovigilance Plan (Including Postauthorization Safety Studies)	• Updated objectives for ongoing category 3 Study 20090522 per current protocol. • Removed completed category 3 Study 20130173.	Version 31.0, 11 January 2023

Part/Module/Annex	Major Change(s)	Version Number and Date
Part V: Risk Minimization Measures (Including Evaluation of the Effectiveness of Risk Minimization Activities)	• Added summary of product characteristics (SmPC) Section 4.8 as a routine risk minimization activity for the important identified risk of hypercalcemia in pediatric patients receiving denosumab and after treatment discontinuation. • Updated Table 33, Additional Risk Minimization Measure: Patient Reminder Card, per template. • Removed completed category 3 Study 20130173 from Table 34, Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern.	Version 31.0, 11 January 2023
Part VI: Summary of the Risk Management Plan	Updated per changes listed above.	Version 31.0, 11 January 2023
Part VII: Annexes		
Annex 2: Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Plan	• Updated objectives for ongoing category 3 Study 20090522 per current protocol. • Updated category 3 Study 20130173 from ongoing to completed.	Version 31.0, 11 January 2023
Annex 3: Protocols for Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan	• Added current protocol for Study 20090522. • Removed protocol for Study 20130173.	Version 31.0, 11 January 2023
Annex 7: Other Supporting Data (Including Referenced Material)	References updated.	Version 31.0, 11 January 2023
Annex 8: Summary of Changes to the Risk Management Plan Over Time	Summary of changes to the risk management plan over time updated.	Version 31.0, 11 January 2023

Other RMP versions under evaluation:	
RMP version number:	N/A
Submitted on:	N/A
Procedure number:	N/A
Details of the currently approved RMP:	
Version number:	30.0
Approved with procedure:	Procedure: EMEA/H/C/001120/II/0093
Date of approval (opinion date):	05 May 2022
Qualified Person for Pharmacovigilance (QPPV) Name:	Raphael Van Eemeren
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorization holder (MAH)´s QPPV. The electronic signature is available on file.

Table of Contents

List of Tables

List of Annexes

List of Abbreviations

Term/Abbreviation	Explanation
ADR	adverse drug reaction
ADT	androgen deprivation therapy
AESI	adverse events of special interest
AFF	atypical femoral fracture
AIDS	acquired immune deficiency syndrome
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
BCVA	best corrected visual acuity
BMD	bone mineral density
COPD	chronic obstructive pulmonary disease
DLP	data lock point
DXA	dual-energy X-ray absorptiometry
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FDA	Food and Drug Administration
GC	glucocorticoid
GIOP	glucocorticoid-induced osteoporosis
HALT	hormone ablation therapy
HIV	human immunodeficiency virus
HR	hazard ratio
IBD	inflammatory bowel disease
IgE	immunoglobulin E
IgG	Immunoglobulin G
INN	International Nonproprietary Name
LHRH	luteinizing hormone releasing hormone
LOCS III	Lens Opacities Classification System III
MAH	marketing authorization holder

Term/Abbreviation	Explanation
MI	myocardial infarction
MOP	male osteoporosis
NO	nuclear opalescence
OI	osteogenesis imperfecta
ONJ	osteonecrosis of the jaw
OPG	osteoprotegerin
OPG-Fc	osteoprotegerin bound to Fc
P	posterior subcapsular
PI	Product Information
PIP	Paediatric Investigation Plan
PMO	postmenopausal osteoporosis
PL	package leaflet
PMR	polymyalgia rheumatica
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	periodic safety update report
PTH	parathyroid hormone
Q3M	every 3 months
Q6M	every 6 months
QD	once a day
QPPV	Qualified Person for Pharmacovigilance
RA	rheumatoid arthritis
RANKL	RANK ligand
RMP	risk management plan
SC	subcutaneous(ly)
SmPC	summary of product characteristics
SOC	system organ class
US	United States
WHO	World Health Organization

PART I. PRODUCT(S) OVERVIEW

Table 1. Product Overview

Active substance(s) (International Nonproprietary Name [INN] or common name)	Denosumab
Pharmacotherapeutic group (Anatomical Therapeutic Chemical [ATC] Code)	M05BX04
Marketing authorization holder	Amgen Europe B.V.
Medicinal products to which this Risk Management Plan (RMP) refers	1
Invented name(s) in the European Economic Area (EEA)	Prolia®
Marketing authorization procedure	Centralized
Brief description of the product	
Chemical class	Denosumab is a fully human monoclonal antibody of the immunoglobulin G (IgG) 2 subclass.
Summary of mode of action	Binds to and neutralizes the activity of the human RANK ligand (RANKL). In blocking RANKL, denosumab reduces osteoclast-mediated bone resorption.
Important information about its composition	Denosumab is a full-length human monoclonal antibody derived from the Xeno-mouse™ technology and produced in Chinese hamster ovary cells.
Hyperlink to the Product Information (PI)	The currently approved PI is provided in Module 1.3.1.
Indication(s) in the EEA	
Current:	Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women, Prolia® significantly reduces the risk of vertebral, non-vertebral and hip fractures. Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. In men with prostate cancer receiving hormone ablation, Prolia significantly reduces the risk of vertebral fractures. Treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture.
Proposed (if applicable)	Not applicable.

Table 1. Product Overview

Dosage in the EEA	
Current:	The recommended dose of Prolia is 60 mg administered as a single subcutaneous (SC) injection once every 6 months (Q6M) into the thigh, abdomen, or upper arm. Patients must be adequately supplemented with calcium and vitamin D.
Proposed (if applicable):	Not applicable.
Pharmaceutical form(s) and strength(s)	
Current (if applicable):	Prolia is supplied as a sterile, preservative-free solution intended for SC use (solution for injection). Prolia is provided in prefilled syringes at a concentration of 60 mg/mL, filled to a target deliverable volume of 1.0 mL.
Proposed (if applicable):	Not applicable.
Is/will the product be subject to additional monitoring in the European Union (EU)?	No

Page 2 of 2

PART II. SAFETY SPECIFICATION

Part II: Module SI - Epidemiology of the Indication(s) and Target Population(s)

Table 2. Summary of Epidemiology of Postmenopausal Osteoporosis

Incidence	The incidence of osteoporosis in women aged ≥ 50 years was 4823 per million per year in Denmark (Vestergaard et al, 2005).
Prevalence	The prevalence of osteoporosis in women in the EU aged ≥ 50 years was 22.1% in 2010, corresponding to approximately 22 100 000 women. Prevalence ranged from 19.3% in Cyprus to 23.4% in Italy. Prevalence increases with age, ranging from 6.3% in women aged 50 - 54 to 47.2% in women aged ≥ 80 years (Hernlund et al, 2013).
Demographics of population in the authorized indication and risk factors for the disease	All patients with PMO are women who have completed menopause. Most women with PMO are ≥ 50 years of age and the incidence of PMO increases with age. Hormone ablation in women with breast cancer causes chemical menopause; these patients may be younger than 50 years of age. Women who have completed menopause are at risk for PMO. Risk factors for osteoporotic fracture include race (risk highest in those of European descent relative to Asian or African descent), lower bone mineral density (BMD), older age, history of previous fractures, parental history of hip fracture, current tobacco smoking, and high alcohol consumption (Cummings et al, 2006; Johnell et al, 2005; Siris et al, 2004; Kanis et al, 2001).
Main existing treatment options	• Calcium and vitamin D supplementation • Weight-bearing and muscle-strengthening exercise • Antiresorptive therapies such as bisphosphonates • Selective estrogen receptor modulators • Hormone replacement therapies • Anabolic treatment: parathyroid hormone (PTH) analogs, PTH-related protein analog (abaloparatide), and strontium ranelate (the latter is both anabolic and antiresorptive)
Natural history of the indicated condition in the untreated population, including mortality and morbidity	Lifetime risk of osteoporotic fracture in women is 40% to 50% (Dennison et al, 2006). Hip fractures often result in disability and loss of independence (Cummings and Melton, 2002; Cree et al, 2000) and approximately 20% of women die within a year of hip fracture (Johnell et al, 2004; Leibson et al, 2002; Cooper et al, 1993). Hormone ablation therapy for women with breast cancer has been shown to be accompanied by increased bone loss (up to 3% per year at the lumbar spine and 2% per year at the total hip) and risk for fracture (11% to 49% increase) (Reid et al, 2008; Coates et al, 2007; Howell et al, 2005; Baum et al, 2003).
Important comorbidities	• Cardiovascular Disease (Ensrud et al, 2010; Bagger et al, 2007; Tanko et al, 2005) • Malignancy (McGlynn et al, 2008; Persson et al, 1994; Olsson and Hagglund, 1992) • Infection (Upala et al, 2016; Dong et al, 2014; Greenspan et al, 2007; United States [US] Food and Drug Administration [FDA], 1997) In women with PMO, therapy for bone loss is generally administered in conjunction with calcium and vitamin D supplementation.

Table 3. Summary of Epidemiology of Male Osteoporosis

Incidence	The incidence of male osteoporosis (MOP) was 862 per million per year in Denmark (Vestergaard et al, 2005).
Prevalence	Prevalence of MOP has been reported at 17.7% in Denmark (Vestergaard et al, 2005) and 2.7% in the United Kingdom (Holt et al, 2002). In the Netherlands, prevalence was 12.1% for men ≥ 55 years of age, with the age-specific prevalence ranging from 15% in men aged 65 to 69 years to 36% in men aged ≥ 85 years (Schuit et al, 2004). North American prevalence tended to be lower (6.3% in Canada [Papaioannou et al, 2008] and 2% to 6% in the United States [Looker et al, 1997]).
Demographics of population in the authorized indication and risk factors for the disease	Compared with PMO, MOP occurs at a slightly older age, and the osteoporosis-related fracture incidence is lower. The consequences of MOP, however, are substantial because the associated fractures result in considerable morbidity and mortality. Primary osteoporosis that results from decreased gonadal function contributes to most PMO and approximately half of MOP; the remainder of MOP is considered secondary due to conditions such as glucocorticoid (GC) use, excess alcohol use, and hyperparathyroidism (Ebeling, 2008; Cauley, 2006).
Main existing treatment options	• Calcium and vitamin D supplementation • Weight-bearing and muscle-strengthening exercise • Antiresorptive therapies such as bisphosphonates • Anabolic treatment: PTH analogs
Natural history of the indicated condition in the untreated population, including mortality and morbidity	Lifetime risk of osteoporosis-related fracture in men has been reported to be between 13% to 22% (Dennison et al, 2006). Post-hip fracture mortality in men is double that of women (Kannegaard et al, 2010; Piirtola et al, 2008; Kiebzak et al, 2002; Center et al, 1999) and the disability from fractures is high (Di Monaco, 2012; Poór et al, 1995).
Important comorbidities	• Cardiovascular disease (Szulc et al, 2009) • Malignancy (Ji et al, 2012; McGlynn et al, 2008) • Infection (Kaufman et al, 2013; Orwoll et al, 2012; Boonen et al, 2009; Figura et al, 2005) In men with osteoporosis, pharmacologic therapy for bone loss is generally administered in conjunction with calcium and vitamin D supplementation.

Table 4. Summary of Epidemiology of Bone Loss Due to Hormone Ablation Therapy in Men With Prostate Cancer

Incidence	In Europe in 2006, it was estimated that > 340 000 men had prostate cancer with over 87 000 deaths (Ferlay et al, 2007). Rates in northern European countries tended to be higher than in southern European countries. Age-standardized incidence rates in Norway, Sweden, Finland, and Denmark were 133.2, 157.2, 149.7, and 80.3 events per 100 000 person-years, respectively, compared with 77.2, 108.4, 101.2, and 81.0 events per 100 000 person-years in Spain, Italy, Portugal, and Greece (Ferlay et al, 2007).
Prevalence	Prevalence of prostate cancer in 12 European countries (Netherlands, Poland, United Kingdom, Italy, Switzerland, Iceland, Norway, Germany, Scotland, Slovakia, Slovenia, and Sweden) in 2003 was 625 per 100 000 (Gatta et al, 2013).
Demographics of population in the authorized indication and risk factors for the disease	Patients with prostate cancer are men, and the incidence of prostate cancer increases with age. Hormone ablation in the form of androgen deprivation therapy (ADT) is frequently used as first-line, second-line, and adjuvant antineoplastic therapy for prostate cancer (Bolla et al, 2002; Messing et al, 1999). Reductions in estrogen and testosterone due to ADT increase risk of bone loss and fracture. Agents used for ADT include luteinizing hormone releasing hormone (LHRH) agonists (eg, leuprorelin, buserelin, histrelin), LHRH antagonists (eg, abarelix, cetrorelix, degarelix), steroidal antiandrogens (eg, megestrol acetate, medroxyprogesterone acetate), and nonsteroidal antiandrogens (eg, bicalutamide, flutamide).
Main existing treatment options	Only Prolia (denosumab 60 mg Q6M) is approved as treatment for bone loss associated with hormone ablation in men with prostate cancer.
Natural history of the indicated condition in the untreated population, including mortality and morbidity	The risk of osteoporotic fracture is increased by approximately 50% in men with prostate cancer who undergo hormone ablation (Shahinian et al, 2005). Risk of osteoporotic fracture increases at the hip, pelvis, extremities, and ribs, as compared with controls (Shahinian et al, 2005; Smith et al, 2005; Melton et al, 2003; Daniell, 1997). The reported 1-year mortality rate after hip fracture in older men is 31% (Campion and Maricic, 2003). Oefelein et al, 2002 reported a negative correlation between fractures at any location and overall survival in men receiving ADT for prostate cancer.
Important comorbidities	• Cardiovascular disease (Li et al, 2012; Martín-Merino et al, 2011; Keating et al, 2006, 2010; Alibhai et al, 2009; D'Amico et al, 2007; Saigal et al, 2007) • Malignancy (Liu et al, 2011; Thellenberg et al, 2003) • Infection (Li et al, 2012) In men with prostate cancer undergoing hormone ablation, therapy for bone loss is generally administered in conjunction with calcium and vitamin D supplementation.

Table 5. Summary of Epidemiology of Glucocorticoid-induced Osteoporosis

Incidence	Glucocorticoid use increases almost linearly with age, from 3.0% at 30 years of age to 3.7% at 50 years, and up to 5.2% at 80 years of age as reported in a meta-analysis that included 42 500 men and women from 7 prospectively studied cohorts across Europe, Canada, the United States, and Australia (Kanis et al, 2004). In the European cohorts included in this meta-analysis, corticosteroid use was reported in 1.9% to 9.2% of women (average age between 64 to 80 years depending on the cohort) and 2.2% to 3.6% of men (average age 65 to 68 years) (Kanis et al, 2004). In the global longitudinal study of osteoporosis in women, which sampled women aged ≥ 55 years from primary care practices in 10 countries, corticosteroid use was reported in 2.7% of women across Europe (Díez-Pérez et al, 2011). In population-based studies in the United Kingdom, between 0.5% to 0.9% of the population was reported to use oral corticosteroids (Fardet et al, 2011; van Staa et al, 2000; Walsh et al, 1996). Oral GCs are estimated to be used by 1.2% of the US population aged ≥ 20 years between 1999 and 2008, and 65% of the GC users reported usage ≥ 90 days (Overman et al, 2013).
Prevalence	A population-based study of general practitioner records in the United Kingdom reported that 0.9% of the population aged 18 years or older used oral GCs. Prevalence of use increased with age from 0.2% among 20 to 29 year olds to 2.5% among 70 to 79 year olds. Long-term use (for 6 months or longer) was seen in 22% of the total population (van Staa et al, 2000). A study from Iceland reported that 0.7% of the population reported receiving long-term treatment with prednisolone (Gudbjornsson et al, 2002). The prevalence of fractures in patients receiving long-term GCs has been reported to be 30% to 50% (Weinstein, 2011).
Demographics of population in the authorized indication and risk factors for the disease	Long-term (≥ 90 days) GC therapy is mostly used in patients diagnosed with joint diseases (rheumatoid arthritis [RA], polymyalgia rheumatica [PMR], and connective tissue diseases), respiratory diseases (asthma and chronic obstructive pulmonary disease [COPD]), and chronic inflammatory bowel disease [IBD]) (Fardet et al, 2011; Saag, 2003; van Staa et al, 2002). Risk factors for glucocorticoid-induced osteoporosis (GIOP) include low body mass index, parental history of hip fracture, current smoking, ≥ 3 alcoholic drinks per day, higher daily GC dose, higher cumulative GC dose, intravenous pulse GC usage, and declining central BMD measurement that exceeds the least significant change (Grossman et al, 2010). Other risk factors include advancing age, underlying disease including RA, PMR, IBD, COPD, and transplantation, GC receptor genotype, and 11beta-hydroxysteroid dehydrogenase isoenzymes (Weinstein, 2011).
Main existing treatment options	Risedronate and zoledronic acid are approved for the prevention of GIOP. Alendronate, risedronate, zoledronic acid, and teriparatide are approved for the treatment of GIOP.

Table 5. Summary of Epidemiology of Glucocorticoid-induced Osteoporosis

Natural history of the indicated condition in the untreated population, including mortality and morbidity	Complications of long-term GC use include osteoporosis (associated with ~2-fold increased risk of fractures [Kanis et al, 2004]), Cushing's syndrome (Gudbjornsson et al, 2002), adrenal suppression, hyperglycemia and diabetes, cardiovascular disease and dyslipidemia, cataracts and glaucoma, dermatological and gastrointestinal events including acute pancreatitis, psychiatric disturbances, and immunosuppression, infectious complications, skin cancer, and non-Hodgkin lymphoma (Liu et al, 2013; Sørensen et al, 2004; Stuck et al, 1989). Treatment with GC > 5 mg/day was significantly associated with an increased mortality in Germany (Listing et al, 2015) and United Kingdom (Movahedi et al, 2016) RA patients, and the association was independent of disease activity. No association between GC use and mortality was found among COPD patients (Kew and Seniukovich, 2014; Walters et al, 2014). No literature describing mortality related to GC use in patients with other common indications was identified. In general, osteoporotic fractures decrease a patient's quality of life by increasing pain, medical costs, and morbidity (Kanis et al, 2007). Excess mortality occurred in both men and women after osteoporotic fractures (Center et al, 1999).
Important comorbidities	• Respiratory diseases (Feldstein et al, 2005; Mudano et al, 2001; van Staa et al, 2000; Walsh et al, 1996) • Joint diseases (Feldstein et al, 2005; Mudano et al, 2001; van Staa et al, 2000; Walsh et al, 1996) • Chronic IBDs: (Feldstein et al, 2005; Mudano et al, 2001; van Staa et al, 2000; Walsh et al, 1996) • Other complications associated with GC use (eg, Cushinghoid features, skin cancer, non-Hodgkin's lymphoma, infectious complications, weight gain, cataracts) (Huscher et al, 2009; Curtis et al, 2006; Sørensen et al, 2004; Proven et al, 2003; Gabriel, 1997; Stuck et al, 1989) In men and women with GIOP, therapy for bone loss is generally administered in conjunction with calcium and vitamin D supplementation. The most common indications for which oral corticosteroids are prescribed include RA (Mudano et al, 2001; Walsh et al, 1996) and COPD (Feldstein et al, 2005; Gudbjornsson et al, 2002; van Staa et al, 2000). Medications used to treat RA include traditional disease modifying antirheumatic drugs such as hydroxychloroquine; leflunomide, methotrexate, and sulfasalazine; tumor necrosis factor inhibitor biologics (such as adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab); non-tumor necrosis factor biologics (such as abatacept, rituximab, or tocilizumab) and tofacitinib (Singh et al, 2016; Alamanos et al, 2006). The percentage of RA patients enrolled in a multinational observational study from 2011 to 2012 treated with methotrexate at baseline ranged from 79% in Italy to 98% in the United Kingdom, and for any biologic therapy from 3% in Uruguay to 77% in the United Kingdom (Dougados et al, 2014).

Table 5. Summary of Epidemiology of Glucocorticoid-induced Osteoporosis

Important comorbidities (continued)	Bronchodilator drugs are regularly used to treat COPD, including short-acting beta2-agonists (such as fenoterol, salbutamol [albuterol], terbutaline) or long-acting beta2-agonists (formoterol, salmeterol), short-acting anticholinergics such as ipratropium bromide, oxitropium bromide or long-acting anticholinergics (tiotropium), and methylxanthines (such as aminophylline, theophylline) (NICE, 2010; Rabe et al, 2007). In a prevalent sample of COPD patients in the United Kingdom (2013), the majority of patients were treated with combination therapy (56%), the most common combination being long-acting anticholinergics, long-acting beta agonists and inhaled corticosteroids (29%) or long-acting beta agonists and inhaled corticosteroids only (20%) (Raluy-Callado et al, 2015).

Part II: Module SII - Nonclinical Part of the Safety Specification

Table 6. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Reproductive toxicity	At area under the curve (AUC) exposures up to 100-fold higher than the human exposure (Q6M), denosumab showed no evidence of impaired fertility in cynomolgus monkeys. In a study of cynomolgus monkeys dosed with denosumab during the period equivalent to the first trimester at AUC exposures up to 99-fold higher than the human dose (Q6M), there was no evidence of maternal or fetal harm. In this study, fetal lymph nodes were not examined. In cynomolgus monkeys dosed with denosumab throughout pregnancy, effects including stillbirths and increased postnatal mortality; abnormal bone growth, reduced hematopoiesis, and tooth malalignment; absence of peripheral lymph nodes; and decreased neonatal growth were noted at AUC exposures up to 119-fold higher than the human exposure (60 mg Q6M). There was no evidence of maternal harm prior to labor; adverse maternal effects occurred infrequently during labor. Maternal mammary gland development was normal. In genetically engineered mice in which RANKL has been turned off by gene removal (a “knockout mouse”), studies suggest absence of RANKL during pregnancy may interfere with maturation of the mammary gland leading to impaired lactation post-partum.	Monkeys exposed to denosumab in utero phenotypically resembled human infants with osteoclast-poor osteopetrosis due to inactivating mutations of RANK or RANKL. Therefore, Prolia is not recommended for use in pregnant women. Women should be advised not to become pregnant during and for at least 5 months after treatment with Prolia. It is not known if Prolia is excreted in human milk. Because denosumab has the potential to cause adverse reactions in nursing infants, a decision should be made on whether to discontinue nursing or discontinue the drug. Use in pregnant and lactating women is not considered a safety concern in this RMP. These populations are not included in the intended indications. In addition, risk minimization via product labelling to avoid pregnancy and breastfeeding is in place.

Table 6. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Developmental toxicity	In neonatal rats, administration of the RANKL inhibitor osteoprotegerin (OPG) bound to Fc (OPG-Fc) resulted in reduced weight gain, reduced bone growth, and inhibited tooth eruption. Despite reductions in bone growth, most bone strength parameters were increased with these treatments. In neonatal cynomolgus monkeys exposed in utero to denosumab at 50 mg/kg, there was increased postnatal mortality; abnormal bone growth resulting in reduced bone strength, reduced hematopoiesis and tooth malalignment; absence of peripheral lymph nodes; and decreased neonatal growth. Following a recovery period from birth out to 6 months of age, the effects on bone generally returned to normal; there were no adverse effects on tooth eruption; and minimal to moderate mineralization in multiple tissues was seen in 1 recovery animal. Adolescent cynomolgus monkeys who received doses of denosumab 150 times the expected clinical exposure had enlargement of epiphyseal growth plates with decreased removal of cartilage matrix in this area, considered to be consistent with the pharmacological activity of denosumab.	Treatment with Prolia may inhibit eruption of dentition in pediatric patients and may impair bone growth in pediatric patients with open growth plates. Prolia is not approved for use in pediatric patients and should not be used in pediatric patients. Risk minimization is in place via product labeling with respect to use in pediatric patients.

Page 2 of 2

Part II: Module SIII - Clinical Trial Exposure

Table 7. Total Subject Exposure to Denosumab (Prolia) in Clinical Trials by Product, Indication, and Duration
Safety Analysis Set

Product Indication	Exposure to Denosumab by Duration										
	≥ 1 Year n (subj-yrs)	≥ 2 Year n (subj-yrs)	≥ 3 Year n (subj-yrs)	≥ 4 Year n (subj-yrs)	≥ 5 Year n (subj-yrs)	≥ 6 Year n (subj-yrs)	≥ 7 Year n (subj-yrs)	≥ 8 Year n (subj-yrs)	≥ 9 Year n (subj-yrs)	≥ 10 Year n (subj-yrs)	Total n (subj-yrs)
Phase 1 studies	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1439 (450.7)
Prolia											
PMO	7519 (38315.3)	5624 (35644.1)	4628 (32994.4)	4003 (30929.7)	3587 (29022.4)	3274 (27327.5)	2339 (20920.0)	1633 (15877.0)	1388 (13826.2)	515 (5173.0)	9640 (40184.5)
MOP	151 (258.2)	27 (54.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	236 (337.9)
HALT	2957 (9634.3)	2159 (8436.1)	1472 (6702.1)	851 (4587.7)	491 (2921.3)	213 (1414.8)	42 (311.8)	0 (0.0)	0 (0.0)	0 (0.0)	3384 (9966.4)
RA	49 (50.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	144 (140.7)
GIOP	366 (833.1)	289 (715.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	416 (866.9)
OI	149 (489.9)	123 (447.7)	96 (376.3)	32 (150.0)	8 (43.6)	2 (12.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	153 (492.4)
Total	11191 (49581.6)	8222 (45297.6)	6196 (40072.8)	4886 (35667.3)	4086 (31987.4)	3489 (28754.6)	2381 (21231.7)	1633 (15877.0)	1388 (13826.2)	515 (5173.0)	13973 (51988.8)
XGEVA total	5723 (18336.3)	3771 (15361.7)	2705 (12774.9)	2046 (10487.2)	523 (3267.5)	168 (1396.4)	96 (932.8)	66 (707.2)	52 (588.0)	42 (493.1)	8768 (19813.1)
Total all studies	16914 (67917.9)	11993 (60659.3)	8901 (52847.7)	6932 (46154.5)	4609 (35254.9)	3657 (30151.0)	2477 (22164.5)	1699 (16584.2)	1440 (14414.2)	557 (5666.1)	24180 (72252.5)

GIOP = glucocorticoid induced osteoporosis; HALT = hormone ablation therapy induced bone loss; MOP = male osteoporosis; n = number of subjects exposed to denosumab; OI = osteogenesis imperfecta; PMO = postmenopausal osteoporosis; RA = rheumatoid arthritis; subj-yrs = total subject-years of exposure

Note: Data from ongoing and completed studies as of 26 September 2022. Ongoing Prolia study included 20140444. Ongoing XGEVA study included 20140114. Only Study 20140444 was blinded at time of reporting. Denosumab exposure for ongoing blinded Study 20140444 is based on the number of subjects dosed and the randomization ratio as specified in the protocol. Safety analysis set includes subjects who received at least 1 dose of investigational product.

For ongoing Prolia studies, subject-years of exposure = (the last exposure date - first non-missing dose date + 1) / 365.25, where last exposure date is the min ((date of last non-missing dose + 180 days - 1), end of study date, data lock point date).

For completed Prolia studies, subject-years of exposure at the subject level was calculated from the first dose date to the (date of last non-missing dose + 180 days).

For ongoing XGEVA studies, subject-years of exposure = (the last exposure date - first non-missing dose date + 1) / 365.25, where last exposure date is the min ((date of last non-missing dose + 28 days - 1), end of study date, data lock point date).

For completed XGEVA studies, subject-years of exposure at the subject level was calculated from the first dose date to the (date of last non-missing dose + 28 days).

For subjects who switched treatment across study periods, subject-years of exposure is calculated in the periods in which the study treatment is received.

Modified from program: /userdata/stat/amg162/meta/pool_studies/analysis/rmp2022/tables/t-exposure-prolia-dur.sas

Output: t14-05-001-001-exposure-prolia-dur.rtf (Date Generated: 27NOV2022:23:16) Source Data: d202209.dsur_exp

Table 8. Total Subject Exposure to Denosumab (Prolia) in Clinical Trials by Product, Age Group, and Gender
Safety Analysis Set

Sex Product Indication	2 to 6 years n (subj-yrs)	7 to 10 years n (subj-yrs)	11 to 17 years n (subj-yrs)	18 to 64 years n (subj-yrs)	65 to 74 years n (subj-yrs)	75 to 84 years n (subj-yrs)	≥ 85 years n (subj-yrs)
Male							
Phase 1 studies	0 (0.0)	0 (0.0)	0 (0.0)	521 (147.8)	32 (12.3)	16 (5.5)	5 (1.5)
Prolia							
PMO	NA	NA	NA	NA	NA	NA	NA
MOP	0 (0.0)	0 (0.0)	0 (0.0)	105 (150.2)	92 (133.6)	39 (54.1)	0 (0.0)
HALT	0 (0.0)	0 (0.0)	0 (0.0)	138 (256.3)	546 (1202.0)	550 (1281.5)	67 (165.9)
RA	0 (0.0)	0 (0.0)	0 (0.0)	36 (35.5)	9 (9.2)	0 (0.0)	0 (0.0)
GIOP	0 (0.0)	3 (4.4)	10 (18.9)	58 (118.6)	41 (84.0)	18 (36.7)	1 (2.6)
OI	17 (49.9)	26 (86.8)	37 (127.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	17 (49.9)	29 (91.2)	47 (145.9)	337 (560.5)	688 (1428.9)	607 (1372.3)	68 (168.5)
XGEVA total	0 (0.0)	0 (0.0)	5 (18.9)	1511 (2730.1)	1171 (1873.5)	816 (1234.1)	128 (204.2)
Total male	17 (49.9)	29 (91.2)	52 (164.9)	2369 (3438.4)	1891 (3314.6)	1439 (2611.9)	201 (374.1)
Female							
Phase 1 studies	0 (0.0)	0 (0.0)	0 (0.0)	780 (249.0)	68 (28.6)	13 (4.7)	4 (1.3)
Prolia							
PMO	0 (0.0)	0 (0.0)	0 (0.0)	2035 (5095.7)	5229 (25200.9)	2270 (9618.2)	106 (269.6)
MOP	NA	NA	NA	NA	NA	NA	NA
HALT	0 (0.0)	0 (0.0)	0 (0.0)	1101 (3826.3)	793 (2649.3)	184 (568.7)	5 (16.3)

Page 1 of 2

Footnotes, including abbreviations, are included in the next page of this table

Table 8. Total Subject Exposure to Denosumab (Prolia) in Clinical Trials by Product, Age Group, and Gender
Safety Analysis Set

Sex Product Indication	2 to 6 years n (subj-yrs)	7 to 10 years n (subj-yrs)	11 to 17 years n (subj-yrs)	18 to 64 years n (subj-yrs)	65 to 74 years n (subj-yrs)	75 to 84 years n (subj-yrs)	≥ 85 years n (subj-yrs)
Female (continued)							
Prolia (continued)							
RA	0 (0.0)	0 (0.0)	0 (0.0)	72 (70.0)	19 (17.9)	7 (7.2)	1 (1.0)
GIOP	0 (0.0)	0 (0.0)	9 (13.4)	143 (315.2)	82 (172.9)	44 (85.5)	7 (14.8)
OI	22 (66.4)	26 (79.7)	24 (79.7)	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	22 (66.4)	26 (79.7)	33 (93.1)	3352 (9310.1)	6123 (28041.0)	2505 (10279.6)	119 (301.7)
XGEVA total	0 (0.0)	0 (0.0)	23 (72.2)	3994 (11308.0)	860 (1941.8)	229 (381.6)	31 (48.7)
Total female	22 (66.4)	26 (79.7)	56 (165.3)	8126 (20867.1)	7051 (30011.4)	2747 (10665.9)	154 (351.7)

GIOP = glucocorticoid induced osteoporosis; HALT = hormone ablation therapy induced bone loss; MOP = male osteoporosis; n = number of subjects exposed to denosumab; OI = osteogenesis imperfecta; PMO = postmenopausal osteoporosis; RA = rheumatoid arthritis; subj-yrs = total subject-years of exposure

Note: Data from ongoing and completed studies as of 26 September 2022. Ongoing Prolia study included 20140444. Ongoing XGEVA study included 20140114. Only Study 20140444 was blinded at time of reporting. Denosumab exposure for ongoing blinded Study 20140444 is based on the number of subjects dosed and the randomization ratio as specified in the protocol. Safety analysis set includes subjects who received at least 1 dose of investigational product.

For ongoing Prolia studies, subject-years of exposure = (the last exposure date - first non-missing dose date + 1) / 365.25, where last exposure date is the min ((date of last non-missing dose + 180 days - 1), end of study date, data lock point date).

For completed Prolia studies, subject-years of exposure at the subject level was calculated from the first dose date to the (date of last non-missing dose + 180 days).

For ongoing XGEVA studies, subject-years of exposure = (the last exposure date - first non-missing dose date + 1) / 365.25, where last exposure date is the min ((date of last non-missing dose + 28 days - 1), end of study date, data lock point date).

For completed XGEVA studies, subject-years of exposure at the subject level was calculated from the first dose date to the (date of last non-missing dose + 28 days).

For subjects who switched treatment across study periods, subject-years of exposure is calculated in the periods in which the study treatment is received.

Modified from program: /userdata/stat/amg162/meta/pool_studies/analysis/rmp2022/tables/t-exposure-prolia-age-sex.sas

Output: t14-05-001-002-exposure-prolia-age-sex.rtf (Date Generated: 27NOV2022:23:16) Source Data: d202209.dsur_exp, r140444.demog_all

Table 9. Exposure to Denosumab (Prolia) in Clinical Trials by Dose Level and Indication
Safety Analysis Set

	Exposure to Denosumab (Prolia) in Years			Subject Exposure to Denosumab (Prolia)		
	< 60 mg n (mean)	60 mg n (mean)	> 60 mg n (mean)	< 60 mg n (subj-yrs)	60 mg n (subj-yrs)	> 60 mg n (subj-yrs)
Phase 1	141 (0.5)	496 (0.5)	159 (0.5)	141 (71.0)	496 (246.5)	159 (78.8)
PMO	233 (1.8)	9437 (4.2)	138 (2.1)	233 (418.8)	9437 (39471.2)	138 (294.5)
MOP	0 (0.0)	236 (1.4)	0 (0.0)	0 (0.0)	236 (337.9)	0 (0.0)
HALT	0 (0.0)	3384 (2.9)	0 (0.0)	0 (0.0)	3384 (9966.4)	0 (0.0)
RA	0 (0.0)	71 (1.0)	73 (1.0)	0 (0.0)	71 (70.6)	73 (70.1)
GIOP	22 (1.7)	394 (2.1)	0 (0.0)	22 (36.7)	394 (830.1)	0 (0.0)
OI	153 (3.2)	0 (0.0)	0 (0.0)	153 (492.4)	0 (0.0)	0 (0.0)
Total	549 (1.9)	14018 (3.6)	370 (1.2)	549 (1018.9)	14018 (50922.8)	370 (443.4)

GIOP = glucocorticoid induced osteoporosis; HALT = hormone ablation therapy induced bone loss; MOP = male osteoporosis; n = number of subjects exposed to denosumab; OI = osteogenesis imperfecta; PMO = postmenopausal osteoporosis; RA = rheumatoid arthritis; subj-yrs = total subject-years of exposure

Note: Data from ongoing and completed studies as of 26 September 2022. Ongoing Prolia study included 20140444. Only Study 20140444 was blinded at time of reporting. Denosumab exposure for ongoing blinded Study 20140444 is based on the number of subjects dosed and the randomization ratio as specified in the protocol. Safety analysis set includes subjects who received at least 1 dose of investigational product.

For ongoing Prolia studies, subject-years of exposure = (the last exposure date - first non-missing dose date + 1) / 365.25, where last exposure date is the min ((date of last non-missing dose + 180 days - 1), end of study date, data lock point date).

For completed Prolia studies, subject-years of exposure at the subject level was calculated from the first dose date to the (date of last non-missing dose + 180 days).

For subjects who switched treatment across study periods, subject-years of exposure is calculated in the periods in which the study treatment is received.

Program: /userdata/stat/amg162/meta/pool_studies/analysis/rmp2022/tables/t-exposure-prolia-dose.sas

Output: t14-05-001-004-exposure-prolia-dose.rtf (Date Generated: 27NOV2022:23:16) Source Data: adam.aslinfo

Table 10. Exposure to Denosumab (XGEVA) in Clinical Trials by Dose Level and Indication
Safety Analysis Set

	Exposure to Denosumab (XGEVA) in Years			Subject Exposure to Denosumab (XGEVA)		
	< 120 mg n (mean)	120 mg n (mean)	> 120 mg n (mean)	< 120 mg n (subj-yrs)	120 mg n (subj-yrs)	> 120 mg n (subj-yrs)
Phase 1	65 (0.1)	554 (0.1)	24 (0.1)	65 (5.2)	554 (46.4)	24 (2.8)
CRPC	0 (0.0)	840 (2.1)	0 (0.0)	0 (0.0)	840 (1771.8)	0 (0.0)
BCAT[a]	0 (0.0)	2241 (3.7)	0 (0.0)	0 (0.0)	2241 (8392.0)	0 (0.0)
GCTB	0 (0.0)	548 (3.7)	0 (0.0)	0 (0.0)	548 (2000.5)	0 (0.0)
HCM	0 (0.0)	33 (0.3)	0 (0.0)	0 (0.0)	33 (10.0)	0 (0.0)
MM	0 (0.0)	95 (0.8)	0 (0.0)	0 (0.0)	95 (72.3)	0 (0.0)
SRE Solid Tumor[b]	84 (0.4)	3351 (1.4)	163 (0.5)	84 (35.7)	3351 (4638.7)	163 (84.0)
SRE MM	0 (0.0)	1268 (2.1)	0 (0.0)	0 (0.0)	1268 (2706.1)	0 (0.0)
NSCLC	0 (0.0)	145 (0.7)	0 (0.0)	0 (0.0)	145 (101.9)	0 (0.0)
Total	149 (0.3)	9075 (2.2)	187 (0.5)	149 (40.9)	9075 (19739.7)	187 (86.8)

BCAT = breast cancer adjuvant therapy; CRPC = castration-resistant prostate cancer; GCTB = giant cell tumor of bone; HCM = hypercalcemia of malignancy; MM = multiple myeloma; n = number of subjects exposed to denosumab; NSCLC = stage IV untreated non-small cell lung carcinoma with or without bone metastasis; SRE = skeletal related events; subj-yrs = total subject-years of exposure.

Note: Data from ongoing and completed XGEVA studies as of 26 September 2022. Ongoing XGEVA study included 20140114. Safety analysis set includes subjects who received at least 1 dose of investigational product.

[a] Study 20060359 (BCAT) dosed XGEVA Q3 or Q4 weeks for 6 months then Q3 months for up to 4.5 years.

[b] Study 20050244 is included in SRE Solid Tumor Category, although the study includes a small portion of MM patients.

For ongoing XGEVA studies, subject-years of exposure = (the last exposure date - first non-missing dose date + 1) / 365.25, where last exposure date is the min ((date of last non-missing dose + 28 days - 1), end of study date, data lock point date).

For completed XGEVA studies, subject-years of exposure at the subject level was calculated from the first dose date to the (date of last non-missing dose + 28 days).

For subjects who switched treatment across study periods, subject-years of exposure is calculated in the periods in which the study treatment is received.

Program: /userdata/stat/amg162/meta/pool_studies/analysis/rmp2022/tables/t-exposure-xgeva-dose.sas

Output: t14-05-001-008-exposure-xgeva-dose.rtf (Date Generated: 27NOV2022:23:16) Source Data: adam.aslinfo

Table 11. Total Subject Exposure to Denosumab (Prolia) in Clinical Trials by Product and Race or Ethnic Group
Safety Analysis Set

Study Type Product Indication	White n (subj-yrs)	Black or African American n (subj-yrs)	Hispanic or Latino n (subj-yrs)	Asian n (subj-yrs)	Other n (subj-yrs)	Missing/ Unknown n (subj-yrs)	Total n (subj-yrs)
Phase 1 studies	1129 (375.4)	186 (32.4)	33 (16.4)	67 (20.0)	24 (6.5)	0 (0.0)	1439 (450.7)
Prolia							
PMO	8721 (37061.3)	79 (332.4)	568 (2400.7)	235 (326.7)	37 (63.4)	0 (0.0)	9640 (40184.5)
MOP	223 (325.7)	1 (1.0)	9 (8.3)	2 (1.9)	1 (1.0)	0 (0.0)	236 (337.9)
HALT	3171 (9453.2)	54 (125.1)	120 (323.0)	26 (48.4)	13 (16.7)	0 (0.0)	3384 (9966.4)
RA	121 (119.6)	4 (3.0)	11 (10.7)	3 (3.0)	5 (4.4)	0 (0.0)	144 (140.7)
GIOP	365 (761.9)	6 (8.4)	0 (0.0)	17 (36.0)	28 (60.6)	0 (0.0)	416 (866.9)
OI	135 (433.0)	2 (7.8)	0 (0.0)	4 (13.7)	12 (37.9)	0 (0.0)	153 (492.4)
Total	12736 (48154.6)	146 (477.7)	708 (2742.7)	287 (429.8)	96 (184.0)	0 (0.0)	13973 (51988.8)
XGEVA total	7082 (15778.9)	317 (696.9)	472 (972.2)	758 (2055.9)	137 (304.1)	2 (5.2)	8768 (19813.1)
Total all studies	20947 (64308.8)	649 (1207.0)	1213 (3731.3)	1112 (2505.7)	257 (494.5)	2 (5.2)	24180 (72252.5)

GIOP = glucocorticoid induced osteoporosis; HALT = hormone ablation therapy induced bone loss; MOP = male osteoporosis; n = number of subjects exposed to denosumab; OI = osteogenesis imperfecta; PMO = postmenopausal osteoporosis; RA = rheumatoid arthritis; subj-yrs = total subject-years of exposure.

Note: Data from ongoing and completed studies as of 26 September 2022. Ongoing Prolia study included 20140444. Ongoing XGEVA study included 20140114. Only Study 20140444 was blinded at time of reporting. Denosumab exposure for ongoing blinded Study 20140444 is based on the number of subjects dosed and the randomization ratio as specified in the protocol. Safety analysis set includes subjects who received at least 1 dose of investigational product.

For ongoing Prolia studies, subject-years of exposure = (the last exposure date - first non-missing dose date + 1) / 365.25, where last exposure date is the min ((date of last non-missing dose + 180 days - 1), end of study date, data lock point date).

For completed Prolia studies, subject-years of exposure at the subject level was calculated from the first dose date to the (date of last non-missing dose + 180 days).

For ongoing XGEVA studies, subject-years of exposure = (the last exposure date - first non-missing dose date + 1) / 365.25, where last exposure date is the min ((date of last non-missing dose + 28 days - 1), end of study date, data lock point date).

For completed XGEVA studies, subject-years of exposure at the subject level was calculated from the first dose date to the (date of last non-missing dose + 28 days).

For subjects who switched treatment across study periods, subject-years of exposure is calculated in the periods in which the study treatment is received.

Program: /userdata/stat/amg162/meta/pool_studies/analysis/rmp2022/tables/t-exposure-prolia-race-ethnic.sas

Output: t14-05-001-003-exposure-prolia-race-ethnic.rtf (Date Generated: 27NOV2022:23:16) Source Data: d202209.dsur_exp

Table 12. Total Subject Exposure to Denosumab (Prolia/XGEVA) in Clinical Trials in Subjects With Renal Impairment
Safety Analysis Set

Product Baseline Calculated Creatinine Clearance[a]	Exposure to Denosumab In Subjects With Serum Creatinine Collected at Baseline n (subj-yrs)
Phase 1 studies	
Mild	270 (98.7)
Moderate	42 (18.7)
Severe	26 (6.7)
Kidney failure	22 (6.1)
Total	360 (130.3)
Prolia	
Mild	6802 (26501.2)
Moderate	3942 (15866.9)
Severe	84 (273.8)
Kidney failure	2 (7.1)
Total	10830 (42648.9)
XGEVA	
Mild	2293 (3806.6)
Moderate	1154 (1681.2)
Severe	36 (50.2)
Kidney failure	2 (1.7)
Total	3485 (5539.7)
Overall total	
Mild	9365 (30406.5)
Moderate	5138 (17566.8)
Severe	146 (330.7)
Kidney failure	26 (14.9)
Total	14675 (48318.9)

kidney failure = < 15 mL/min; mild = 60 to < 90 mL/min; moderate = 30 to < 60 mL/min; n = number of subjects exposed to denosumab; severe =15 to < 30 mL/min; subj-yrs = total subject-years of exposure

Note: Data from ongoing and completed studies as of 26 September 2022. Ongoing Prolia study included 20140444. Ongoing XGEVA study included 20140114. Only Study 20140444 was blinded at time of reporting. Denosumab exposure for ongoing blinded Study 20140444 is based on the number of subjects dosed and the randomization ratio as specified in the protocol. Safety analysis set includes subjects who received at least 1 dose of investigational product.

[a] Baseline calculated creatinine clearance estimated by the Cockcroft-Gault equation = (140 - age in years) x weight in kg [x 0.85 if female] / (72 x serum creatinine in mg/dL).

For ongoing Prolia studies, subject-years of exposure = (the last exposure date - first non-missing dose date + 1) / 365.25, where last exposure date is the min ((date of last non-missing dose + 180 days - 1), end of study date, data lock point date).

For completed Prolia studies, subject-years of exposure at the subject level was calculated from the first dose date to the (date of last non-missing dose + 180 days).

For ongoing XGEVA studies, subject-years of exposure = (the last exposure date - first non-missing dose date + 1) / 365.25, where last exposure date is the min ((date of last non-missing dose + 28 days - 1), end of study date, data lock point date).

For completed XGEVA studies, subject-years of exposure at the subject level was calculated from the first dose date to the (date of last non-missing dose + 28 days).

For subjects who switched treatment across study periods, subject-years of exposure is calculated in the periods in which the study treatment is received.

Program: /userdata/stat/amg162/meta/pool_studies/analysis/rmp2022/tables/t-exposure-renal.sas
Output: t14-05-001-009-exposure-renal.rtf (Date Generated: 27NOV2022:23:16) Source Data: adam.aslinfo

Part II: Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Table 13. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale (if not included as missing information)
Contraindications			
Hypocalcemia	Hypocalcemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy. Patients receiving denosumab must have adequate intake of calcium and vitamin D. This information is provided in the Summary of Product Characteristics (SmPC).	No	It is a contraindication in the SmPC.
Hypersensitivity to the active substance or to any of the excipients	Patients who are hypersensitive to denosumab or to any of the excipients listed in Section 6.1 of the SmPC should not receive Prolia.	No	It is a contraindication in the SmPC.
Exclusion Criteria Applying to PMO, HALT, and GIOP Studies			
BMD T-score < -4.0	It was considered unethical to enroll subjects with a T-score < -4.0 in placebo-controlled studies when approved therapies were available, because these subjects would remain untreated for 3 years if randomized to the placebo group.	No	The safety and efficacy of denosumab is not expected to differ in subjects with lower BMD T-scores. In subgroup analyses by baseline lumbar spine and total hip T-score for the range of T-scores enrolled in the large pivotal PMO study (20030216), denosumab was effective in each subgroup. Therefore, no special dosing recommendations for patients with BMD T-scores < -4.0 are considered necessary. Furthermore, subjects with BMD T-scores < -4.0 were not excluded from the pivotal study in the GIOP population (Study 20101217) because the study was active-controlled (risedronate).

Page 1 of 3

Footnotes, including abbreviations, are included on the last page of this table

Table 13. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale (if not included as missing information)
Exclusion Criteria Applying to PMO, HALT, and GIOP Studies (continued)			
Other bone diseases	Patients with other bone diseases such as RA, OI, and Paget's disease were excluded from the pivotal osteoporosis studies because other bone diseases could confound the efficacy results.	No	Prolia is not indicated for use in these other patient populations. However, subjects with RA were not excluded from the pivotal study in the GIOP population (Study 20101217), because RA is a common indication for GC use.
Exclusion Criteria Applying to Osteoporosis Studies Only			
Previous bisphosphonate treatment	Subjects with previous bisphosphonate treatment were excluded from pivotal osteoporosis studies in accordance with regulatory guidance to demonstrate fracture benefit in a PMO population. Because bisphosphonates incorporate into bone and long-term use of bisphosphonates is associated with continued effects of the drug after treatment is stopped, it was deemed most appropriate to exclude previous bisphosphonate treatment.	No	In Study 20050234, a double-blind, alendronate-controlled, in postmenopausal women with low BMD who had received bisphosphonates for at least 6 months preceding study entry, safety results were similar in the denosumab and alendronate treatment groups. In addition, Studies 20080099, 20080562, and 20110153 evaluated the effects of denosumab and a bisphosphonate (risedronate, ibandronate, or zoledronic acid, respectively) in postmenopausal women transitioning from previous bisphosphonate therapy. There were no new safety findings in these studies.
Evidence of distant metastases	Subjects with distant metastases have been evaluated in other clinical studies of denosumab using a different dose and schedule (up to 120 mg monthly).	No	An indication in this patient population was not sought for denosumab 60 mg. XGEVA (denosumab 120 mg) is approved for prevention of skeletal-related events in adults with bone metastases from solid tumors; thus, safety in this population is well documented.

Page 2 of 3

Footnotes, including abbreviations, are included on the last page of this table

Table 13. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale (if not included as missing information)
Exclusion Criteria Applying to HALT Studies Only			
Serum creatinine > 2.0 mg/dL	Treatment with antiresorptive agents reduces the ability to mobilize calcium from bone; thus, hypocalcemia could be exacerbated in patients with renal impairment.	No	Study 20040245 demonstrated that renal impairment does not affect the pharmacokinetics of denosumab; therefore, no dose adjustments are required in patients with impaired renal function. Recommendations for adequate intake of calcium and vitamin D in all patients, and recommendations for monitoring of serum calcium in patients predisposed to hypocalcemia, have been included in the SmPC. No other special dosing recommendations are considered necessary for subjects with renal impairment.
Exclusion Criteria Applying to All Indications			
Subjects who are pregnant or breastfeeding, or planning to become pregnant	Adequate and well-controlled studies with denosumab have not been conducted in pregnant women due to the potential risk to the fetus. It is not known whether denosumab is transferred into human milk.	No	These populations are not included in the intended indications. Risk minimization via product labelling instructing patients to avoid pregnancy and breast feeding is in place. No additional pharmacovigilance activities or additional risk minimization are warranted.

Page 3 of 3

BMD = bone mineral density; GC = glucocorticoid; GIOP = glucocorticoid-induced osteoporosis; HALT = hormone ablation therapy induced bone loss; OI = osteogenesis imperfecta; PMO = postmenopausal osteoporosis; RA = rheumatoid arthritis; SmPC = summary of product characteristics

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

Based on the number of subjects exposed, the duration of subject exposure, the total dose of Prolia and the mechanism of action, the Prolia clinical development program is able to detect rare adverse drug reactions (ADRs), as well as ADRs associated with prolonged exposure or long latency.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programs

Table 14. Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Eight pregnancies have been reported in the clinical development program.
Breastfeeding women	No cases of lactation have been reported in the clinical development program.
Patients with relevant comorbidities	
Patients with hepatic impairment	Not included in the clinical development program.
Patients with renal impairment	Subjects with renal impairment were not specifically excluded from Prolia clinical studies. A total of 6802 subjects (26 501.2 subject-years), 3942 subjects (15 866.9 subject-years), 84 subjects (273.8 subject-years), and 2 subjects (7.1 subject-years) with mild, moderate, or severe renal impairment, or kidney failure, respectively, were exposed to Prolia in the clinical development program.
Patients with cardiovascular impairment	In a large pivotal PMO study (20030216), a substudy was conducted in 2363 subjects with high cardiovascular risk.
Immunocompromised patients	No specific exclusions with exception of human immunodeficiency virus (HIV) positive patients.
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program.
Population with relevant different ethnic origin	A total of 12 736 subjects (48 154.6 subject-years), 146 subjects (477.7 subject-years), 708 subjects (2742.7 subject-years), and 287 subjects (429.8 subject-years) of white, black or African American, Hispanic or Latino, or Asian race/ethnicity, respectively, were exposed to Prolia in the clinical development program. In pivotal studies, 451 of 4910 subjects who received denosumab belonged to an ethnic or racial minority (PMO: 321/4050; HALT 130/860).
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.

Page 1 of 2

Footnotes, including abbreviations, are on the next page of this table

Table 14. Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Other	
Pediatric patients	Male: A total of 17 subjects (49.9 subject-years), 29 subjects (91.2 subject-years), and 47 subjects (145.9 subject-years) aged 2 to 6 years, 7 to 10 years, and 11 to 17 years, respectively, were exposed to Prolia, in the clinical development program. Female: A total of 22 subjects (66.4 subject-years), 26 subjects (79.7 subject-years), and 33 subjects (93.1 subject-years) aged 2 to 6 years, 7 to 10 years, and 11 to 17 years, respectively, were exposed to Prolia, in the clinical development program.
Geriatric patients	This population has not been underrepresented in the clinical development program (see Table 8). Male: A total of 688 subjects (1428.9 subject-years), 607 subjects (1372.3 subject-years), and 68 subjects (168.5 subject-years) aged 65 to 74 years, 75 to 84 years, and ≥ 85 years, respectively, were exposed to Prolia, in the clinical development program. Female: A total of 6123 subjects (28041.0 subject-years), 2505 subjects (10279.6 subject-years), and 119 subjects (301.7 subject-years) aged 65 to 74 years, 75 to 84 years, and ≥ 85 years, respectively, were exposed to Prolia, in the clinical development program.
Patients with BMD T-score < -4.0	Subjects with BMD T-score < -4.0 were not explicitly excluded from Prolia clinical studies, except Study 20030216.

Page 2 of 2

BMD = bone mineral density; HALT = hormone ablation therapy; PMO = postmenopausal osteoporosis

Part II: Module SV - Postauthorization Experience

SV.1 Postauthorization Exposure

SV.1.1 Method Used to Calculate Exposure

The estimated cumulative number of patient-years of exposure and patients exposed to Prolia through commercial distribution are shown in Table 15 and Table 16, respectively. Cumulatively through 26 September 2022, the total worldwide postmarketing patient exposure in Amgen and business partner territories was 33 161 236 patient-years.

SV.1.2 Exposure

Table 15. Estimated Number of Patient-years of Exposure to Denosumab (Prolia, CORORA) in the Postmarketing Setting, by Region and Demographic Characteristics

Demographic Characteristic[a]	Cumulative[b] Number of Patient-years of Exposure					
	AU	CA	EUR	US	Other[c]	Total
Overall	2903246	1553291	11686873	7376108	5526297	29045814
Sex						
Female	2573934	1372675	10284213	6515102	4951634	25697560
Male	329312	180617	1402659	861004	574663	3348254
Age						
18 - 34	4830	2724	21878	13040	7540	50011
35 - 49	76890	43215	345651	206769	121886	794410
50 - 64	800534	446503	3539160	2133928	1309311	8229435
65 - 74	895101	464319	3349597	2193999	1875592	8778609
≥ 75	1125892	596531	4430587	2828372	2211968	11193349
Sex/age						
Female						
18 - 34	4152	2349	18932	11251	6403	43089
35 - 49	69256	38984	312367	186566	109078	716249
50 - 64	726728	405117	3209029	1935977	1191195	7468044
65 - 74	804956	415375	2974309	1961050	1712410	7868100
≥ 75	968843	510851	3769577	2420261	1932548	9602078
Male						
18 - 34	676	375	2945	1789	1138	6924
35 - 49	7636	4231	33284	20204	12807	78161
50 - 64	73709	41340	329850	197739	117856	760494
65 - 74	90243	48989	375569	233162	163442	911404
≥ 75	157049	85681	661010	408111	279421	1591271

AU = Australia and New Zealand; CA = Canada; EUR = Europe (European Union, European Economic Area, Switzerland, and the United Kingdom); Other = countries, not otherwise specified, where Amgen is the marketing authorization holder; US = United States

Note: Numbers may not add to the total due to rounding.

[a] Age and sex breakdowns are based on patient characteristics in MarketScan and Optum, US health insurance claims databases. Applying these distributions to regions outside the United States requires strong assumptions that are not easily testable.

[b] Cumulatively through 26 September 2022

[c] Does not include Japan

Table 16. Estimated Number of Patients Exposed to Denosumab (Prolia, CORORA) in the Postmarketing Setting, by Region and Demographic Characteristics

Demographic Characteristic[a]	Cumulative[b] Number of Patients Exposed					
	AU	CA	EUR	US	Other[c]	Total
Overall	2087514	1160033	9097040	5585318	3626854	21556759
Sex						
Female	1833760	1016279	7944625	4890552	3214937	18900154
Male	253755	143753	1152415	694766	411916	2656603
Age						
18 - 34	4009	2315	18948	11229	6050	42550
35 - 49	63246	36432	297474	176644	96301	670098
50 - 64	645363	369900	3003940	1791783	1002222	6813210
65 - 74	587738	317581	2407859	1520438	1116464	5950080
≥ 75	787157	433806	3368820	2085223	1405816	8080821
Sex/age						
Female						
18 - 34	3475	2009	16481	9751	5202	36917
35 - 49	57195	32978	269561	159929	86746	606409
50 - 64	585020	335190	2720988	1623540	909796	6174534
65 - 74	520186	279600	2105971	1337148	1003767	5246672
≥ 75	667886	366502	2831625	1760184	1209426	6835624
Male						
18 - 34	536	305	2467	1478	846	5631
35 - 49	6052	3453	27914	16715	9556	63689
50 - 64	60299	34688	282820	168144	92307	638259
65 - 74	67597	38002	302019	183389	112819	703826
≥ 75	119271	67305	537195	325040	196390	1245199

AU = Australia and New Zealand; CA = Canada; EUR = Europe (European Union, European Economic Area, Switzerland, and the United Kingdom); Other = countries, not otherwise specified, where Amgen is the marketing authorization holder; US = United States

Note: Numbers may not add to the total due to rounding.

[a] Age and sex breakdowns are based on patient characteristics in MarketScan and Optum, US health insurance claims databases. Applying these distributions to regions outside the United States requires strong assumptions that are not easily testable.

[b] Cumulatively through 26 September 2022

[c] Does not include Japan

Postauthorization Use From Business Partners

The estimated cumulative exposure (as of 26 September 2022) in Daiichi Sankyo and GlaxoSmithKline territories was 4 103 981 patient-years and 11 441 patient-years, respectively.

Part II: Module SVI - Additional EU Requirements for the Safety Specification

SVI.1 Potential for Misuse for Illegal Purposes

No evidence to suggest a potential for drug abuse or misuse has been observed.

Part II: Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable, as this is not the initial RMP for the product. Please refer to the full safety profile in the SmPC.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable, as this is not the initial RMP for the product. Please refer to the full safety profile in the SmPC.

SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

There are no new safety concerns or reclassification of safety concerns.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Table 17. Important Identified Risk: Hypocalcemia

Potential mechanisms	Denosumab inhibits osteoclast bone resorption, thereby decreasing the release of calcium from bone into the bloodstream.
Evidence source(s) and strength of evidence	This risk was identified in the phase 3, randomized, double-blind, placebo- or active-controlled studies.
Characterization of the risk	
Frequency	In the pooled pivotal studies for PMO and HALT subject incidence of hypocalcemia adverse events was < 0.1% in denosumab-treated subjects and 0.1% in placebo-treated subjects. The incidence of hypocalcemia adverse events was lower in denosumab-treated subjects than in placebo-treated subjects; thus, 95% CIs were not calculated. In the 24-month final analysis of the GIOP study, subject incidence of hypocalcemia adverse events was 0.3% in the denosumab group; there were no adverse events of hypocalcemia in the risedronate group thus, 95% CIs were not calculated.
Severity	While most hypocalcemia events are mild to moderate in severity; severe events have occurred.
Reversibility	Hypocalcemia is reversible when treated with oral calcium and vitamin D supplementation. In severe cases, IV calcium supplementation may be required.
Long-term outcomes	No long-term complications are anticipated for properly treated hypocalcemia.
Impact on quality of life	For severe symptomatic hypocalcemia, patients may be hospitalized for treatment. Generally, patients recover when their hypocalcemia is treated.
Risk factors and risk groups	Risk factors include severe renal impairment and hyperphosphatemia. Other risks factors may include a history of hypoparathyroidism, PTH resistance, vitamin D deficiency or resistance, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, severe renal impairment (CrCL < 30 mL/min), dialysis, and some medications (Finkelstein, 2001).
Preventability	Pre-existing hypocalcemia should be corrected by adequate intake of calcium and vitamin D before initiating therapy, and supplementation with calcium and vitamin D is important during therapy in all patients receiving denosumab. Clinical monitoring of calcium levels is recommended during treatment, especially in those with renal impairment.

Page 1 of 2

Footnotes, including abbreviations, are defined on last page of this table

Table 17. Important Identified Risk: Hypocalcemia

Impact on the risk-benefit balance of the product	The risk of hypocalcemia has been considered in the product benefit-risk assessment. In light of the product labeling addressing this risk, the overall benefit-risk balance is considered to be positive.
Public health impact	Significant public health impact is not expected as this risk is preventable and treatable with the appropriate risk mitigating measures communicated clearly in the SmPC.

Page 2 of 2

CrCL = creatinine clearance; GIOP = glucocorticoid-induced osteoporosis; HALT = hormone ablation therapy; IV = intravenous; PMO = postmenopausal osteoporosis; PTH = parathyroid hormone; SmPC = summary of product characteristics

Table 18. Important Identified Risk: Skin Infection Leading to Hospitalisation

Potential mechanisms	Keratinocytes can express RANKL and blocking RANKL in mice decreased the number of regulatory T-cells in skin, leading to an increased inflammatory response (Loser et al, 2006; Yamaguchi and Sakaguchi, 2006).
Evidence source(s) and strength of evidence	This risk was identified in the phase 3, randomized, double-blind, placebo- or active-controlled studies.
Characterization of the risk	
Frequency	In pooled PMO/HALT pivotal studies, subject incidence of skin infection was 1.4% with denosumab and 1.3% with placebo; the hazard ratio (HR) was 1.09 (95% CI: 0.78, 1.53). Subject incidence of serious adverse events of skin infection was 0.4% with denosumab and 0.2% with placebo (HR [95% CI] = 2.55 [1.13, 5.76]). In the 24-month final analysis of the GIOP study, subject incidence of adverse events of skin infection was 1.8% with denosumab and 0.5% with risedronate; the HR was 3.62 (95% CI = 0.75, 17.42). Subject incidence of serious adverse events of skin infection was 0.5% in both the denosumab and risedronate groups (HR [95% CI] = 1.03 [0.15, 7.34]).
Severity	Serious adverse events of skin infection were mostly severe in intensity.
Reversibility	These events typically resolved with administration of antibiotics.
Long-term outcomes	No long-term complications are anticipated for properly treated patients who are hospitalized due to skin infections.
Impact on quality of life	Requires a hospital stay; patients generally recover with antibiotic treatment.
Risk factors and risk groups	Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, HIV/acquired immune deficiency syndrome (AIDS), immunosuppressant drugs (eg, corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition. Risk factors for skin infection in older patients include skin wounds, peripheral vascular disease, eczema/dermatitis, and venous stasis disorders.
Preventability	No preventive measures are known.
Impact on the risk-benefit balance of the product	The risk of skin infection leading to hospitalisation has been considered in the product benefit-risk assessment. In light of the product labeling addressing this risk, the overall benefit-risk balance is considered to be positive.
Public health impact	Since frequency of skin infection leading to hospitalisation is relatively low, absolute difference between denosumab and placebo groups is relatively small, and the adverse events can be effectively treated by antibiotics, the negative impact to public health is relatively small.

GIOP = glucocorticoid-induced osteoporosis; HALT = hormone ablation therapy; PMO = postmenopausal osteoporosis; RANKL = RANK ligand

Table 19. Important Identified Risk: Osteonecrosis of the Jaw

Potential mechanisms	Osteonecrosis of the jaw (ONJ) appears to be multifactorial and multiple hypotheses have been postulated and have included factors such as inhibition of bone remodeling, infection and inflammation, inhibition of angiogenesis, soft tissue toxicity, altered immunity and genetic predisposition. As yet, evidence supporting these hypotheses has been variable and little is understood in how these multiple pathways might interact (Fassio et al, 2017; Aghaloo et al, 2015).
Evidence source(s) and strength of evidence	This risk was identified in open-label long-term extensions to phase 3, randomized, double-blind, placebo-controlled studies.
Characterization of the risk	
Frequency	No cases of ONJ have been reported in placebo-controlled studies (although cases were reported in open-label extensions to the pivotal PMO study and a HALT study); thus, 95% CIs were not calculated. No cases of ONJ were reported in the GIOP study. Overall, across the Amgen-sponsored clinical development program for Prolia, positively adjudicated ONJ cases have been reported rarely (18 ONJ cases in 23 552 subjects, 0.076%) in subjects cumulatively exposed to denosumab (60 mg) clinical studies.
Severity	Most events leading to adjudication as ONJ were assessed as moderate in severity. Mild and severe events were also reported.
Reversibility	In general, ONJ events are clinically reversible with supportive care, antibiotics; however, surgical treatment may be required.
Long-term outcomes	No data on long-term outcomes are available.
Impact on quality of life	Discomfort associated with ONJ lesions and/or with more extensive treatments may impact patient wellbeing via decreased oral intake (eg, decreased hydration and decreased nutritional intake).
Risk factors and risk groups	Risk factors include duration of exposure to denosumab, prior bisphosphonate use (particularly for extended periods of time), older age, periodontal disease, dentoalveolar surgery, trauma from poorly fitting dentures, malignancy, chemotherapy, corticosteroids, smoking, systemic or regional infection, immune-compromised state predisposing to increased risk of infection, hypercoagulable state secondary to underlying malignancy, and vascular insufficiency due to thrombosis (Mehrotra and Ruggiero, 2006; Ruggiero et al, 2006).
Preventability	A dental examination with appropriate preventive dentistry is recommended prior to treatment with Prolia, especially in patients with risk factors. While on treatment, patients should avoid invasive dental procedures where possible. Patients who are suspected of having or who develop ONJ while on Prolia should receive care by a dentist or an oral surgeon. In patients who develop ONJ during treatment with Prolia, a temporary interruption of treatment should be considered based on individual risk/benefit assessment until the condition resolves.

Page 1 of 2

Footnotes, including abbreviations, are defined on last page of this table

Table 19. Important Identified Risk: Osteonecrosis of the Jaw

Impact on the risk-benefit balance of the product	The risk of osteonecrosis of the jaw has been considered in the product benefit-risk assessment. In light of the product labeling and additional risk minimization activities addressing this risk, the overall benefit-risk balance is considered to be positive.
Public health impact	Significant public health impact is not expected with Prolia, as the event is rare and the actions taken to minimize the likelihood of developing ONJ are described in the prescribing information.

Page 2 of 2

GIOP = glucocorticoid-induced osteoporosis; HALT = hormone ablation therapy; ONJ = osteonecrosis of the jaw; PMO = postmenopausal osteoporosis

Table 20. Important Identified Risk: Hypersensitivity Reactions

Potential mechanisms	Two types of allergic reactions, immunoglobulin E (IgE)- and non-IgE-mediated, appear to be related to monoclonal antibody administration. The IgE-mediated reactions can cause both wheal and flare reactions at the injection site, but may also be associated with urticaria and anaphylaxis. The mechanism of non-IgE reactions is unclear.
Evidence source(s) and strength of evidence	This risk was identified in the postmarketing setting based on a clinically plausible association between administration of denosumab and hypersensitivity reactions.
Characterization of the risk	
Frequency	In the pooled PMO/HALT pivotal studies, subject incidence of hypersensitivity and drug hypersensitivity was 1.0% in denosumab-treated subjects and 0.8% in placebo-treated subjects; HR = 1.26 (95% CI: 0.83, 1.90). Subject incidence of potential clinical consequences of hypersensitivity was 1.3% in both treatment groups; HR = 0.94 (95% CI: 0.66, 1.33). In the 24-month final analysis of the GIOP study, subject incidence of adverse events potentially associated with hypersensitivity was 6.3% in denosumab-treated subjects and 4.7% in risedronate-treated subjects (HR [95% CI] = 1.41 [0.77, 2.59]).
Severity	Most hypersensitivity reactions are mild to moderate in severity; severe events have occurred.
Reversibility	Hypersensitivity reactions are generally reversible with discontinuation of the medication, though treatment may be required.
Long-term outcomes	No long-term complications are anticipated for properly treated hypersensitivity reactions.
Impact on quality of life	For severe hypersensitivity reactions, patients may be treated in the emergency room and/or hospitalized for treatment. Generally, patients recover when denosumab is discontinued with or without additional treatment.
Risk factors and risk groups	Known hypersensitivity to denosumab and any of its excipients
Preventability	No data are available on potential measures to prevent hypersensitivity reactions to denosumab. The appropriate contraindication information on hypersensitivity to denosumab and any of its excipients is included in the SmPC.
Impact on the risk-benefit balance of the product	The risk of hypersensitivity reactions has been considered in the product benefit-risk assessment. In light of the product labeling addressing this risk, the overall benefit-risk balance is considered to be positive.
Public health impact	No significant public health impact is expected as reports of severe events (eg, anaphylaxis) are rare.

GIOP = glucocorticoid-induced osteoporosis; HALT = hormone ablation therapy; HR = hazard ratio; IgE = immunoglobulin E; PMO = postmenopausal osteoporosis; PT = preferred term; SmPC = Summary of Product Characteristics

Table 21. Important Identified Risk: Atypical Femoral Fracture

Potential mechanisms	Prolonged suppression of bone turnover may be associated with increased risk of atypical femoral fracture (AFF), but the pathogenesis remains unclear and the causes of AFF are likely multi-factorial. Based on nonclinical studies, collagen cross-linking and maturation, accumulation of microdamage and advanced glycation end products, mineralization, remodeling, vascularity, and angiogenesis lend biologic plausibility to a potential association between these effects and AFF (Ismail et al, 2018; Shane et al, 2010).
Evidence source(s) and strength of evidence	This risk was identified in an open-label long-term extension to a phase 3, randomized, double-blind, active-controlled study.
Characterization of the risk	
Frequency	No cases of confirmed AFF have been reported in placebo-controlled studies; thus, 95% CIs were not calculated. In the GIOP study, subject incidence of confirmed AFF was 0.3% (1 event) in the denosumab group; there were no adverse events of AFF in the risedronate group thus, 95% CIs were not calculated. Overall, as of 26 September 2016, adjudicated-positive cases of AFF have been reported rarely (5 of 23 280 subjects, 0.021%) in subjects exposed to denosumab (60 mg) in clinical studies.
Severity	Atypical femoral fracture is a medically important adverse event that generally requires significant medical interventions such as surgery and ongoing monitoring to mitigate risk for and severity of contralateral fractures. The few events from Prolia studies leading to adjudication of AFF were considered as severe in intensity.
Reversibility	Atypical femoral fracture is generally treatable with surgical intervention. It is unknown if the pathophysiological mechanism(s) contributing to the development of AFF are reversible after treatment is discontinued.
Long-term outcomes	No data on long-term outcomes are available.
Impact on quality of life	As with other femur fractures, AFF can cause short-term or long-term disability. Some data suggests that healing of AFF may be more prolonged than a typical femoral fracture (Bubbear, 2016; Unnanuntana et al, 2013).
Risk factors and risk groups	Long-term antiresorptive treatment has been associated with AFF. Corticosteroids have also been reported in the literature to potentially be associated with AFF (Meier et al, 2012; Giusti et al, 2011). Atypical femoral fractures have also been reported in patients with certain comorbid conditions (eg, vitamin D deficiency, RA, hypophosphatasia) and with use of bisphosphonates, glucocorticoids, and proton pump inhibitors (Shane et al, 2010).

Page 1 of 2

Footnotes, including abbreviations, are defined on last page of this table

Table 21. Important Identified Risk: Atypical Femoral Fracture

Preventability	No data are currently available on potential measures to prevent AFF. Patients using long-term antiresorptives may experience pain over the femur, which requires radiological examination if atypical fracture is suspected.
Impact on the risk-benefit balance of the product	The risk of atypical femoral fracture has been considered in the product benefit-risk assessment. In light of the product labeling addressing this risk, the overall benefit-risk balance is considered to be positive.
Public health impact	Based on the infrequency of AFF in patients treated with denosumab, no significant additional public health impact is expected.

Page 2 of 2

AFF = atypical femoral fracture; GIOP = glucocorticoid-induced osteoporosis; RA = rheumatoid arthritis

Table 22. Important Identified Risk: Hypercalcemia in Pediatric Patients Receiving Denosumab and After Treatment Discontinuation

Potential mechanisms	The exact mechanism of hypercalcemia occurring in pediatric patients both during the dosing interval and following discontinuation is not certain but may be a consequence of the following, alone, or in combination: • Hypercalcemia may result from rapid resorption of retained primary spongiosa in a skeleton with active endochondral ossification. The rate of endochondral ossification and duration of exposure to denosumab would determine the amount of accumulated primary spongiosa that could influence the magnitude of resorptive response (mechanostat-driven) and release of calcium from resorbing bone matrix via an autocrine/paracrine mechanism. • The magnitude of the resorptive response following treatment and withdrawal in the immature skeleton could be dictated by the normal high rate of bone turnover in individuals with growing skeletons. • The response of the osteoclast lineage to loss of inhibition of osteoclastogenesis may be intrinsically more robust in individuals with growing skeletons. The increased skeletal metabolism related to bone modeling and growth in children is therefore likely to impact the frequency of hypercalcemia occurring both between the dosing interval and following discontinuation.
Evidence source(s) and strength of evidence	Data to evaluate safety concern were derived from Prolia clinical trials in pediatric subjects with OI, XGEVA clinical studies, and postmarketing adverse event reporting involving pediatric patients receiving denosumab at unapproved doses and/or unapproved indications for use.
Characterization of the risk	
Frequency	In the completed pediatric OI Study 20130173 during the Q6M dosing regimen, hypercalcemia (Amgen Medical Dictionary for Regulatory Activities [MedDRA] Query [Narrow Search; AMQN]) was reported for 29 subjects (19.0%). All these events were nonserious. During the Q3M dosing regimen and following denosumab discontinuation, hypercalcemia (AMQN) was reported for 22 subjects (36.7%). Serious adverse events of hypercalcemia were reported for 8 subjects (13.3%).
Severity	Most subjects in the pediatric OI Study 20130173 receiving the Q3M dosing regimen who had hypercalcemia events experienced mild events. Grade ≥ 3 hypercalcemia was reported for 10 subjects (16.7%). Grade 4 (life-threatening) hypercalcemia was reported for 4 subjects (6.7%).
Reversibility	Hypercalcemia is reversible when treated. In severe cases, use of rescue medications may be required.
Long-term outcomes	No long-term adverse effects are anticipated for properly treated hypercalcemia.

Page 1 of 2

Footnotes, including abbreviations, are defined on last page of this table

Table 22. Important Identified Risk: Hypercalcemia in Pediatric Patients Receiving Denosumab and After Treatment Discontinuation

Characterization of the risk (continued)	
Impact on quality of life	Pediatric patients may present with severe hypercalcemia requiring hospitalization. Generally, patients recover when the hypercalcemia is treated.
Risk factors and risk groups	Pediatric patients with growing skeletons and high bone turnover disease states (such as OI).
Preventability	Prolia is not indicated in pediatric patients (age < 18 years) and should not be used in pediatric patients. If used in a clinical trial setting, such as for pediatric GIOP, monitoring for signs and symptoms and periodic serum calcium is advisable.
Impact on the risk-benefit balance of the product	The benefit-risk profile of Prolia (denosumab) is not favorable in the pediatric patient population.
Public health impact	Significant public health impact is not expected as this risk is preventable with the appropriate risk mitigating measures communicated clearly in the SmPC.

Page 2 of 2

AMQN = Amgen MedDRA Query (Narrow Search); GIOP = glucocorticoid-induced osteoporosis; MedDRA = Medical Dictionary for Regulatory Activities; OI = osteogenesis imperfecta; Q3M = every 3 months; Q6M = every 6 months; SmPC = Summary of Product Characteristics

Table 23. Important Potential Risk: Fracture Healing Complications

Potential mechanisms	Because denosumab directly suppresses bone resorption and (indirectly) bone formation, it has the theoretical potential to delay fracture healing.
Evidence source(s) and strength of evidence	This is a theoretical risk based on the mechanism of action.
Characterization of the risk	
Frequency	Of the subjects who had nonvertebral fractures in the large pivotal PMO study, fracture healing complications (delayed healing or nonunion) were reported in 2 of 386 subjects in the denosumab group (0.5%) and 5 of 465 subjects (1.1%) in the placebo group. Of the subjects who had nonvertebral fractures in the pivotal study for HALT-breast cancer, fracture healing complications were reported in 0 of 8 subjects in the denosumab group and 1 of 8 subjects (12.5%) in the placebo group. Because of the low incidence of fracture healing complications, 95% CIs were not calculated. No fracture healing complications were reported in the MOP study. No fracture healing complications were reported in the GIOP study.
Severity	This risk has not been substantiated; however, impaired fracture healing could have significant impact on patient wellbeing.
Reversibility	This risk has not been substantiated; however, the effects of denosumab on osteoclasts are fully reversible.
Long-term outcomes	This risk has not been substantiated; however, no long-term impact would be anticipated based on reversibility.
Impact on quality of life	Fracture healing complications can cause short-term or long-term disability. Surgery may be required.
Risk factors and risk groups	General risk factors for fracture healing complications are thought to include older age, diabetes, use of medications such as non-steroidal anti-inflammatory drugs and corticosteroids, smoking, excessive alcohol use, and poor nutrition (Hernandez et al, 2012; Gaston and Simpson, 2007).
Preventability	No preventive measures are known.
Impact on the risk-benefit balance of the product	The potential risk of fracture healing complications has been considered in overall assessment supporting a positive benefit-risk profile.
Public health impact	No significant impact on public health is anticipated.

GIOP = glucocorticoid-induced osteoporosis; HALT = hormone ablation therapy; MOP = male osteoporosis; PMO = postmenopausal osteoporosis

Table 24. Important Potential Risk: Infection

Potential Mechanisms	RANK ligand is expressed on activated T and B cells and in the lymph nodes and some reports have described immune modulatory effects of RANKL inhibition. However, no clinically relevant effect of denosumab treatment was observed on peripheral blood immune cell subset profiles in studies in healthy elderly men, postmenopausal women, and postmenopausal women with low BMD. No evidence of a treatment effect of denosumab on immunoglobulin production was observed.
Evidence source(s) and strength of evidence	This is considered a potential risk based on theoretical concerns which has not been substantiated in the extensive clinical study program or in the postmarketing experience.
Characterization of the risk	
Frequency	

	Subject Incidence[a] (percent)	Hazard ratio (95% CI)
Adverse events		
Placebo	50.6	0.98 (0.92, 1.03)
Denosumab	50.1	
Serious adverse events		
Placebo	3.4	1.25 (1.02, 1.53)
Denosumab	4.3	
Serious adverse events not including skin infection		
Placebo	3.3	1.18 (0.95, 1.45)
Denosumab	3.9	
Opportunistic infection[b]		
Placebo	0.1%	--
Denosumab	0.1%	

[a] Pooled pivotal studies for PMO (20030216, 20040132) and HALT and 20040138 in prostate cancer and 20040135 in breast cancer, Safety Analysis Set.

In the 24-month final analysis of the GIOP study, subject incidence of infections was 36.3% with denosumab and 36.4% with risedronate; HR = 1.06 (0.84, 1.34). Subject incidence of serious adverse events of infection was 5.8% in the denosumab group and 6.5% in the risedronate group (HR [95% CI] = 0.95 [0.54, 1.68]).

Severity	The majority of reported events of infection were non serious. Serious adverse events were most commonly reported as severe in intensity.
Reversibility	Infections when treated appropriately are generally reversible.
Long-term outcomes	Infection generally responds to appropriate treatment and as such no long-term effects are anticipated.
Impact on quality of life	For severe infection, patients may be hospitalized for treatment. Generally, patients recover when their infection is treated

Page 1 of 2

Footnotes, including abbreviations, are defined on last page of this table

Table 24. Important Potential Risk: Infection

Risk factors and risk groups	Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, HIV/AIDS, immunosuppressant drugs (eg, corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition.
Preventability	No preventive measures are known.
Impact on the risk-benefit balance of the product	The potential risk of infection has been considered in the overall assessment which supports a positive benefit-risk profile in the indicated populations.
Public health impact	No significant public health impact is expected for this unsubstantiated risk as effective treatments are available.

Page 2 of 2

AIDS = Acquired immune deficiency syndrome; GIOP = glucocorticoid-induced osteoporosis; HALT = hormone ablation therapy; HIV = Human immunodeficiency virus; HR = hazard ratio; PMO = postmenopausal osteoporosis; RANKL = RANK ligand; SmPC = summary of product characteristics

Table 25. Important Potential Risk: Cardiovascular Events

Potential mechanisms	Elevated levels of OPG have been associated with coronary artery disease in cross-sectional studies but this association has been contradicted by preclinical and epidemiological studies demonstrating that the lack of OPG or unopposed RANKL is associated with cardiac calcification. Because of these conflicting results and because denosumab inhibits RANKL, a theoretical concern for denosumab to affect progression of atherosclerosis exists.
Evidence source(s) and strength of evidence	This is a theoretical risk based on epidemiological data demonstrating elevated OPG in patients with cardiovascular disease.
Characterization of the risk	
Frequency	In a pooled analysis of the large pivotal PMO study (20030216) and the pivotal HALT-prostate study, the overall subject incidence of adjudicated-positive serious cardiovascular events was 5.8% with denosumab and 5.6% with placebo (HR [95% CI] = 1.00 [0.85, 1.19]). The subject incidence of positively adjudicated, pre-defined categories of serious cardiovascular event was comparable between the treatment groups in the pooled analysis, as shown below:

Studies 20030216 and 20040138[a]	Subject Incidence (percent)	Hazard ratio (95% CI)
Acute coronary syndrome		
Placebo	1.4	0.96 (0.68, 1.35)
Denosumab	1.4	
Congestive heart failure		
Placebo	0.7	1.03 (0.64, 1.65)
Denosumab	0.8	
Stroke/transient ischemic attack		
Placebo	1.5	1.06 (0.77, 1.46)
Denosumab	1.7	
Arrhythmia		
Placebo	1.3	1.15 (0.82, 1.63)
Denosumab	1.5	
Other vascular disorders		
Placebo	0.9	1.13 (0.75, 1.71)
Denosumab	1.1	
Cardiovascular death		
Placebo	1.1	0.79 (0.52, 1.18)
Denosumab	0.9	

[a] Safety Analysis Set

Footnotes, including abbreviations, are defined on last page of this table

Table 25. Important Potential Risk: Cardiovascular Events

Characterization of the Risk (continued)	
Frequency (continued)	During the placebo-controlled phase of the pivotal study for MOP, adverse events in the cardiac disorders system organ class (SOC) were reported in 8 (6.7%) denosumab-treated and 3 (2.5%) placebo-treated subjects (note: 2 events of angina tonsillitis in the denosumab group were incorrectly coded to the cardiac disorders adverse event category). The incidence of adverse events in the vascular disorders SOC was 5.0% in denosumab-treated and 6.7% in placebo-treated subjects. In the GIOP study, adverse events in the cardiovascular disorders or vascular disorders SOC were reported in 65 (16.5%) denosumab-treated subjects and 53 (13.8%) risedronate-treated subjects (HR [95% CI] = 1.27 [0.88, 1.82]). Subject incidence of serious adverse events in the cardiovascular or vascular SOC was 3.8% on the denosumab group and 3.9% in the risedronate group. In Study 20190038 (a retrospective cohort study assessing the incidence of cardiovascular and cerebrovascular events among postmenopausal women and men with osteoporosis treated with denosumab or zoledronic acid for up to 36 months of treatment), the unadjusted incidence rates of myocardial infarction, stroke, and MI-stroke composite outcome were 0.23 to 0.72 per 100 person-years. The differences in the unadjusted incidence rates of outcome between denosumab and zoledronic acid treatment groups were small (< 0.1 risk difference).
Severity	This risk has not been substantiated; however, cardiovascular events may be severe/life-threatening.
Reversibility	This risk has not been substantiated; however, effects of denosumab to block RANKL are fully reversible.
Long-term outcomes	This risk has not been substantiated; however, cardiovascular events could impact patient long-term outcome.
Impact on quality of life	Cardiovascular disease varies greatly in severity. For severe disease, patients may be hospitalized for treatment and disability may occur.

Page 2 of 3

Footnotes, including abbreviations, are defined on last page of this table

Table 25. Important Potential Risk: Cardiovascular Events

Risk factors and risk groups	The denosumab development program comprises studies of older subject populations (eg, osteoporosis, cancer) that are likely to have a higher incidence of pre-existing cardiovascular conditions and, thus, a higher incidence of cardiovascular toxicities than that of the general population (Schulz et al, 2004; Hak et al, 2000). Risk factors for atherosclerosis include age, sex, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes, and concomitant medications, including antipsychotic agents and COX-2 inhibitors (Murphy and Dargie, 2007; Smith et al, 2004).
Preventability	No preventive measures are known.
Impact on the risk-benefit balance of the product	The potential risk of cardiovascular events has been considered in overall assessment supporting a positive benefit-risk profile.
Public health impact	Significant public health impact of Prolia on cardiovascular disease severity or incidence is not anticipated.

Page 3 of 3

GIOP = glucocorticoid-induced osteoporosis; HALT = hormone ablation therapy; HR = hazard ratio; MOP = male osteoporosis; OPG = osteoprotegerin; PMO = postmenopausal osteoporosis; RANKL = RANK ligand; SOC = system organ class

Table 26. Important Potential Risk: Malignancy

Potential mechanisms	RANK ligand is expressed on activated T and B cells and in the lymph nodes and some reports have described immune modulatory effects of RANKL inhibition; however, in vitro studies of RANK and RANKL activity on a wide range of human tumor types provide no evidence for carcinogenic risk associated with RANKL inhibition (Armstrong et al, 2008; Jones et al, 2006; Mori et al, 2007). In in vivo rodent cancer models, RANKL inhibition has been shown to have a beneficial effect (Branstetter et al, 2008; Canon et al, 2008a, 2008b; Vanderkerken et al, 2003; Yonou et al, 2003; Zhang et al, 2001). If denosumab did affect immune function, a hypothetical association with malignancies linked to immune modulation could exist and would be expected to show the pattern of malignancy associated with immune deficiency.
Evidence source(s) and strength of evidence	This is considered a potential risk based on theoretical concerns and has not been substantiated in the extensive clinical study program or in the postmarketing experience.
Characterization of the risk	
Frequency	In the large pivotal PMO study (20030216), the subject incidence of new primary malignancy was 4.8% with denosumab and 4.3% with placebo (HR [95% CI] = 1.11 [0.90, 1.37]). In the pivotal HALT prostate cancer study (20040138), the subject incidence of new primary malignancy was 5.1% with denosumab and 4.6% with placebo (HR [95% CI] = 1.08 [0.67, 1.72]), and overall survival was 94.1% in each treatment group (HR [95% CI] = 0.99 [0.65, 1.52]). During the placebo-controlled phase of the MOP study, 4 subjects in the denosumab group (3.3%) and no subject in the placebo group reported events of malignancy. The events were prostate cancer in 3 subjects and basal cell carcinoma in 1 subject. Two prostate cancer cases were likely present at baseline based on past medical history. In the 24-month final analysis of the GIOP study, subject incidence of malignancy was 3.0% with denosumab and 1.8% with risedronate (HR [95% CI] = 1.75 [0.69, 4.44]). Subject incidence of serious adverse events of malignancy was 1.8% with denosumab and 1.6% with risedronate.
Severity	Malignancy is a clinically important event requiring medical intervention.
Reversibility	Although some malignancies will respond to treatment, long-term survival will depend upon multiple factors and as such onset of malignancy is rarely considered reversible.
Long-term outcomes	New primary malignancy or progression of existing malignancy may be fatal, life-threatening and long-term outcomes will likely be impacted.
Impact on quality of life	Malignancy can be life-threatening and generally requires intervention eg, surgery, radiation, and/or chemotherapy.

Page 1 of 2

Footnotes, including abbreviations, are defined on last page of this table

Table 26. Important Potential Risk: Malignancy

Risk factors and risk groups	General factors for risk of malignancy include advancing age, diet, cigarette smoking, excessive ethanol consumption, and numerous environmental toxins. In addition, cancer populations are at increased risk for a second primary malignancy because of their existing malignancy, possible genetic predisposition, and exposure to chemotherapy and radiation treatment (Anand et al, 2008; World Health Organization [WHO], 2010).
Preventability	No preventive measures are known.
Impact on the risk-benefit balance of the product	The potential risk of malignancy has been considered in the product benefit-risk assessment which supports a positive benefit-risk profile in the indicated populations.
Public health impact	Significant public health impact is not anticipated.

Page 2 of 2

CI = confidence interval; GIOP = glucocorticoid-induced osteoporosis; HALT = hormone ablation therapy; HR = hazard ratio; MOP = male osteoporosis; PMO = postmenopausal osteoporosis; RANKL = RANK ligand

SVII.3.2 Presentation of the Missing Information

There is no missing information for Prolia (denosumab).

Part II: Module SVIII - Summary of the Safety Concerns

Table 27. Summary of Safety Concerns

Important identified risks	• Hypocalcemia • Skin infection leading to hospitalisation • Osteonecrosis of the jaw • Hypersensitivity reactions • Atypical femoral fracture • Hypercalcemia in pediatric patients receiving denosumab and after treatment discontinuation
Important potential risks	• Fracture healing complications • Infection • Cardiovascular events • Malignancy
Missing information	• None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORIZATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection are presented in Table 28 and Table 29.

Table 28. Specific Adverse Reaction Follow-up Questionnaires

Follow-up Questionnaire (Annex 4)	Safety Concern(s)	Purpose
Hypocalcemia	Hypocalcemia	To monitor the nature of hypocalcemia in patients treated with Prolia in the postmarketing environment.
Infection	Skin infection leading to hospitalisation Infection	To monitor the nature of skin infections leading to hospitalisation and infections of any type reported in patients treated with Prolia in the postmarketing environment.
Osteonecrosis of the jaw	Osteonecrosis of the jaw	To monitor the nature of ONJ in patients treated with Prolia in the postmarketing environment.
Postmarketing reports of potential atypical fracture	Atypical femoral fracture	To monitor the nature of AFF reported in patients treated with Prolia in the postmarketing environment.
Fracture healing	Fracture healing complications	To monitor the nature of fracture healing complications reported in patients treated with Prolia in the postmarketing environment.
Malignancy	Malignancy	To monitor the nature of malignancy adverse events reported in patients treated with Prolia in the postmarketing environment.
Hypersensitivity	Hypersensitivity reactions	To monitor the nature of hypersensitivity reported in patients treated with Prolia in the postmarketing environment.

Table 29. Other Forms of Routine Pharmacovigilance Activities

Description of Activity	Safety Concern(s)	Objectives	Milestones
• Potential events of ONJ, reported in clinical trials, may be referred for external adjudication, if appropriate for the trial. • Potential postmarketing study reports undergo independent medical review to confirm cases of ONJ, if specified in the protocol.	Osteonecrosis of the jaw	• To collect further information on the rate of ONJ in clinical studies • To monitor the nature of ONJ in patients treated with Prolia in the postmarketing environment	Not applicable
• Potential cases of AFF from clinical trial setting may be referred for external adjudication, if appropriate for the trial. • Potential postmarketing study reports undergo independent medical review to confirm cases of AFF if specified in the protocol.	Atypical femoral fracture	• To collect further information on the rate of AFF in clinical studies • To monitor the nature of AFF in patients treated with Prolia in the postmarketing environment	Not applicable

III.2 Additional Pharmacovigilance Activities

Table 30. Category 1 to 3 Postauthorization Safety Studies

Study Short Name, Study Title and Category Number	Rationale and Study Objectives	Study Design	Study Population	Milestones
20090522 Postmarketing observational study Denosumab global safety assessment among women with postmenopausal osteoporosis (PMO), men with osteoporosis, and men and women who receive Prolia with glucocorticoid exposure in multiple observational databases Category 3	Rationale: A favorable benefit-risk profile of denosumab 60 mg Q6M (Prolia®) for the treatment of PMO and bone loss associated with hormone ablation in men with prostate cancer was characterized in the original marketing application, which was approved by EMA on 26 May 2010. Amgen also committed to conduct a long-term observational study in administrative databases to prospectively evaluate the incidence of adverse events of special interest (AESI) in postmenopausal women administered Prolia (denosumab). Additional target populations have been added for use of denosumab in men with osteoporosis, and in men and women who receive Prolia with glucocorticoid-induced osteoporosis. Objectives: • Determine incidence rates of AESI in women with PMO exposed to denosumab, women with PMO exposed to bisphosphonates, and among all women with PMO • Describe characteristics, clinical features, and AESI risk factors in women with PMO exposed to denosumab, women with PMO exposed to bisphosphonates, and all women with PMO • Compare the incidence of the AESI in women with PMO exposed to denosumab to that in women with PMO exposed to bisphosphonates	Women: A prospective open cohort study. Men: A prospective fixed cohort study.	Postmenopausal women; women with PMO; patients who receive Prolia for unapproved indications; men with osteoporosis, treated with denosumab, and men and women who receive Prolia with glucocorticoid exposure.	Annual reporting from 05 December 2014 Final report: Q3 2023

Table 30. Category 1 to 3 Postauthorization Safety Studies

Study Short Name, Study Title and Category Number	Rationale and Study Objectives	Study Design	Study Population	Milestones
20090522 Postmarketing observational study Denosumab global safety assessment among women with postmenopausal osteoporosis (PMO), men with osteoporosis, and men and women who receive Prolia with glucocorticoid exposure in multiple observational databases Category 3 (continued)	• Describe incidence rates of AESI in postmenopausal women • Describe denosumab utilization patterns in subjects who receive denosumab therapy for treatment of PMO • Describe Prolia utilization patterns in subjects who receive Prolia therapy for unapproved indications (indication, dosage, frequency) • In men with osteoporosis treated with denosumab, describe subject characteristics, clinical features, AESI risk factors, subject follow-up, incidence rates of AESI, and denosumab utilization patterns (US Medicare and Optum Research Database) • In men and women who receive Prolia with glucocorticoid exposure, describe subject characteristics, clinical features, AESI risk factors, subject follow-up, incidence rates of AESI, and denosumab utilization patterns (US Medicare and Optum Research Database) <u>Safety concerns addressed:</u> Hypocalcemia, osteonecrosis of the jaw, atypical femoral fracture, fracture healing complications, infection, hypersensitivity reactions, malignancy			

III.3 Summary Table of Additional Pharmacovigilance Activities

There are no ongoing or planned category 1 or 2 studies. Ongoing and planned category 3 studies are presented below in Table 31.

Table 31. Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required additional pharmacovigilance activities				
20090522 Postmarketing observational study Denosumab global safety assessment among women with postmenopausal osteoporosis (PMO), men with osteoporosis, and men and women who receive Prolia with glucocorticoid exposure in multiple observational databases Ongoing	• Determine incidence rates of AESI in women with PMO exposed to denosumab, women with PMO exposed to bisphosphonates, and among all women with PMO • Describe characteristics, clinical features, and AESI risk factors in women with PMO exposed to denosumab, women with PMO exposed to bisphosphonates, and all women with PMO • Compare the incidence of the AESI in women with PMO exposed to denosumab to that in women with PMO exposed to bisphosphonates • Describe incidence rates of AESI in postmenopausal women • Describe denosumab utilization patterns in subjects who receive denosumab therapy for treatment of PMO • Describe Prolia utilization patterns in subjects who receive Prolia therapy for unapproved indications (indication, dosage, frequency) • In men with osteoporosis treated with denosumab, describe subject characteristics, clinical features, AESI risk factors, subject follow-up, incidence rates of AESI, and denosumab utilization patterns (US Medicare and Optum Research Database)	Hypocalcemia, osteonecrosis of the jaw, atypical femoral fracture, fracture healing complications, infection, hypersensitivity reactions, malignancy.	Annual reporting Final report	From 05 December 2014 Q3 2023

Table 31. Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required additional pharmacovigilance activities (continued)				
20090522 (continued) Postmarketing observational study Denosumab global safety assessment among women with postmenopausal osteoporosis (PMO), men with osteoporosis, and men and women who receive Prolia with glucocorticoid exposure in multiple observational databases Ongoing	• In men and women who receive Prolia with glucocorticoid exposure, describe subject characteristics, clinical features, AESI risk factors, subject follow-up, incidence rates of AESI, and denosumab utilization patterns (US Medicare and Optum Research Database)			

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

Not applicable

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

Risk Minimization Plan

V.1 Routine Risk Minimization Measures

Table 32. Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Identified Risks	
Hypocalcemia	Routine risk communication: • SmPC Section 4.2, 4.3, 4.4, and 4.8 • Package leaflet (PL) Section 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation for correction of hypocalcemia prior to initiating treatment with Prolia and clinical monitoring of calcium levels during treatment with Prolia is included in SmPC Section 4.4.
Skin infection leading to hospitalisation	Routine risk communication: • SmPC Section 4.4 and 4.8 • PL Section 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • None
Osteonecrosis of the jaw	Routine risk communication: • SmPC Section 4.4 and 4.8 • PL Section 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation for oral examination, maintenance of good oral hygiene during treatment, management of patients with unavoidable invasive dental procedures, and temporary interruption of treatment if ONJ occurs is included in SmPC Section 4.4.
Hypersensitivity reactions	Routine risk communication: • SmPC Section 4.3 and 4.8 • PL Section 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • None

Page 1 of 2

Footnotes, including abbreviations, are defined on the last page of this table.

Table 32. Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Identified Risks (Continued)	
Atypical femoral fracture	Routine risk communication: • SmPC Section 4.4 and 4.8 • PL Section 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation for reporting new or unusual thigh, hip, or groin pain is included in SmPC Section 4.4.
Hypercalcemia in pediatric patients receiving denosumab and after treatment discontinuation	Routine risk communication: • SmPC Section 4.2, 4.4, and 4.8 • PL Section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: • None
Important Potential Risks	
Fracture healing complications	Routine risk communication: • SmPC Section 5.3 Routine risk minimization activities recommending specific clinical measures to address the risk: • None
Infection	Routine risk communication: • SmPC Section 4.8 • PL Section 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • None
Cardiovascular events	Routine risk communication: • None Routine risk minimization activities recommending specific clinical measures to address the risk: • None
Malignancy	Routine risk communication: • None Routine risk minimization activities recommending specific clinical measures to address the risk: • None
Missing Information	
None	

Page 2 of 2

ONJ = osteonecrosis of the jaw; PL = package leaflet; SmPC = summary of product characteristics.

V.2 Additional Risk Minimization Measures

Table 33. Additional Risk Minimization Measure: Patient Reminder Card

Objectives	Patient reminder cards will be provided to address the following risk: • Osteonecrosis of the jaw
Rationale for the additional risk minimization activity	The purpose of the patient reminder card is to remind patients about important safety information that they need to be aware of before and during treatment with denosumab (Prolia®) injections for osteoporosis and bone loss, including: • the risk of osteonecrosis of the jaw during treatment with Prolia; • the need to highlight any problems with their mouth or teeth to their doctors/nurses before starting treatment; • the need to ensure good oral hygiene during treatment; • the need to inform their dentist of treatment with Prolia and to contact their doctor or dentist if problems with the mouth or teeth occur during treatment.
Target audience and planned distribution path	Target audience will be the patients. The patient reminder card was distributed to prescribers with instruction to provide it to patients. The patient reminder card is distributed by mail and prescribers are provided with contact details to request additional copies of the card. Some national plans include making the patient reminder card available on a website.
Plans to evaluate the effectiveness of the interventions and criteria for success	Monitor and evaluate postmarketing and clinical study safety data and report in periodic safety update reports (PSURs). The distribution of the patient reminder card will be tracked to ensure that it is distributed in accordance with the plan agreed with national agencies. Additional requests for patient reminder cards and web downloads will also be recorded as an indicator of ongoing use of the patient reminder card. The effectiveness of risk minimization of ONJ in the EU will be monitored through postmarket reporting rates of ONJ before and after introduction of the patient reminder card compared to the rest of the world.
Evaluation of the effectiveness of risk minimization activities	No change in risk-benefit profile

EU = European Union; ONJ = osteonecrosis of the jaw; PSUR = periodic safety update report

V.3 Summary of Risk Minimization Measures

Table 34. Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks		
Hypocalcemia	Routine risk minimization measures: • SmPC Section 4.4, where recommendation regarding correction and monitoring of calcium levels is provided • SmPC Section 4.2, 4.3, and 4.8 • PL Section 2 and 4 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for hypocalcemia Additional pharmacovigilance activities: • Postmarketing observational Study 20090522
Skin infection leading to hospitalisation	Routine risk minimization measures: • SmPC Section 4.4 and 4.8 • PL Section 2 and 4 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for infection Additional pharmacovigilance activities: • Postmarketing observational Study 20090522
Osteonecrosis of the jaw	Routine risk minimization measures: • SmPC Section 4.4, where oral hygiene and dental management guidance is provided • SmPC Section 4.8 • PL Section 2 and 4 Additional risk minimization measures: • Patient reminder card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for ONJ • External adjudication of events reported in clinical trials • Independent medical review of postmarketing study reports Additional pharmacovigilance activities: • Postmarketing observational Study 20090522

Page 1 of 3

Footnotes, including abbreviations, are defined on the last page of this table.

Table 34. Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks (continued)		
Hypersensitivity reactions	Routine risk minimization measures: • SmPC Section 4.3 and 4.8 • PL Section 2 and 4 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for hypersensitivity Additional pharmacovigilance activities: • Postmarketing observational Study 20090522
Atypical femoral fracture	Routine risk minimization measures: • SmPC Section 4.4, where recommendation for reporting potential symptoms is provided • SmPC Section 4.8 • PL Section 2 and 4 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for AFF • External adjudication of clinical trial cases • Independent medical review of postmarketing study reports Additional pharmacovigilance activities: • Postmarketing observational Study 20090522
Hypercalcemia in pediatric patients receiving denosumab and after treatment discontinuation	Routine risk minimization measures: • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Important Potential Risks		
Fracture healing complications	Routine risk minimization measures: • SmPC Section 5.3 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for fracture healing complications Additional pharmacovigilance activities: • Postmarketing observational Study 20090522

Footnotes, including abbreviations, are defined on the last page of this table.

Table 34. Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Potential Risks (continued)		
Infection	Routine risk minimization measures: • SmPC Section 4.8 • PL Section 4 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for infection Additional pharmacovigilance activities: • Postmarketing observational Study 20090522
Cardiovascular events	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Malignancy	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for malignancy Additional pharmacovigilance activities: • Postmarketing observational Study 20090522
Missing Information		
None		

Page 3 of 3

AFF = atypical femoral fracture; ONJ = osteonecrosis of the jaw; PL = package leaflet; SmPC = summary of product characteristics.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

A summary of the RMP for Prolia (denosumab) is presented below.

Summary of Risk Management Plan for Prolia® (denosumab)

This is a summary of the risk management plan (RMP) for Prolia. The RMP details important risks of Prolia, how these risks can be minimized, and how more information will be obtained about Prolia's risks and uncertainties (missing information).

Prolia's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Prolia should be used.

This summary of the RMP for Prolia should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Prolia's RMP.

I. The Medicine and What it is Used for

Prolia is authorized for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures, the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures, and treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture (see SmPC for the full indication). It contains denosumab as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of Prolia's benefits can be found in Prolia's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage: https://www.ema.europa.eu/medicines/human/EPAR/prolia.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Prolia®, together with measures to minimize such risks and the proposed studies for learning more about Prolia's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;

- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the public (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In the case of Prolia, these measures are supplemented with *additional risk minimization measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including periodic safety update report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Prolia is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of Prolia are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Prolia. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of important risks and missing information	
Important identified risk	• Hypocalcemia • Skin infection leading to hospitalisation • Osteonecrosis of the jaw • Hypersensitivity reactions • Atypical femoral fracture • Hypercalcemia in pediatric patients receiving denosumab and after treatment discontinuation
Important potential risk	• Fracture healing complications • Infection • Cardiovascular events • Malignancy
Missing information	• None

II.B. Summary of Important Risks

Important identified risk: Hypocalcemia	
Evidence for linking the risk to the medicine	This risk was identified in the phase 3, randomized, double-blind, placebo- or active-controlled studies.
Risk factors and risk groups	Risk factors include severe renal impairment and hyperphosphatemia. Other risks factors may include a history of hypoparathyroidism, parathyroid hormone resistance, vitamin D deficiency or resistance, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, severe renal impairment (creatinine clearance < 30 mL/min), dialysis, and some medications (Finkelstein, *Cecil Essentials of Medicine, 5th ed*, 2001:639-648).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4, where recommendation regarding correction and monitoring of calcium levels is provided • SmPC Section 4.2, 4.3, and 4.8 • PL Section 2 and 4 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Postmarketing observational Study 20090522 See Section II.C of this summary for an overview of the postauthorization development plan

Important identified risk: Skin infection leading to hospitalisation	
Evidence for linking the risk to the medicine	This risk was identified in the phase 3, randomized, double-blind, placebo- or active-controlled studies.
Risk factors and risk groups	Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), immunosuppressant drugs (eg, corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition. Risk factors for skin infection in older patients include skin wounds, peripheral vascular disease, eczema/dermatitis, and venous stasis disorders.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4, and 4.8 • PL Section 2 and 4 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Postmarketing observational Study 20090522 See Section II.C of this summary for an overview of the postauthorization development plan

Important identified risk: Osteonecrosis of the jaw	
Evidence for linking the risk to the medicine	This risk was identified in open-label long-term extensions to phase 3, randomized, double-blind, placebo-controlled studies.
Risk factors and risk groups	Risk factors include duration of exposure to denosumab, prior bisphosphonate use (particularly for extended periods of time), older age, periodontal disease, dentoalveolar surgery, trauma from poorly fitting dentures, malignancy, chemotherapy, corticosteroids, smoking, systemic or regional infection, immune-compromised state predisposing to increased risk of infection, hypercoagulable state secondary to underlying malignancy, and vascular insufficiency due to thrombosis (Mehrotra and Ruggiero, *Hematology*, 2006;356-360; Ruggiero et al, *J Oncol Pract*, 2006;2:7-14).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4, where oral hygiene and dental management guidance is provided • SmPC Section 4.8 • PL Section 2 and 4 Additional risk minimization measures: • Patient reminder card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Postmarketing observational Study 20090522 See Section II.C of this summary for an overview of the postauthorization development plan

Important identified risk: Hypersensitivity reactions	
Evidence for linking the risk to the medicine	This risk was identified in the postmarketing setting based on a clinically plausible association between administration of denosumab and hypersensitivity events.
Risk factors and risk groups	Known hypersensitivity to denosumab and any of its excipients.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.3 and 4.8 • PL Section 2 and 4 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Postmarketing observational Study 20090522 See Section II.C of this summary for an overview of the postauthorization development plan

Important identified risk: Atypical Femoral Fracture	
Evidence for linking the risk to the medicine	This risk was identified in an open-label long-term extension to a phase 3, randomized, double-blind, active-controlled study.
Risk factors and risk groups	Long-term antiresorptive treatment has been associated with atypical femoral fracture. Corticosteroids have also been reported in the literature to potentially be associated with atypical femoral fracture (Meier et al, *Arch Intern Med*, 2012;172:930-936; Giusti et al, *Bone*, 2011; 48[5]:966-971). Atypical femoral fractures have also been reported in patients with certain comorbid conditions (eg, vitamin D deficiency, rheumatoid arthritis, hypophosphatasia) and with use of bisphosphonates, glucocorticoids, and proton pump inhibitors (Shane et al, *J Bone Miner Res*, 2010;25:2267-2294).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4, where recommendation for reporting potential symptoms is provided • SmPC Section 4.8 • PL Section 2 and 4 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Postmarketing observational Study 20090522 See Section II.C of this summary for an overview of the postauthorization development plan

Important identified risk: Hypercalcemia in pediatric patients receiving denosumab and after treatment discontinuation	
Evidence for linking the risk to the medicine	Data to evaluate safety concerns derived from Prolia clinical trials in pediatric subjects with osteogenesis imperfecta, XGEVA clinical studies and postmarketing adverse event reporting involving pediatric patients receiving denosumab at unapproved doses and/or unapproved indications for use.
Risk factors and risk groups	Pediatric patients with growing skeletons and high bone turnover disease states (such as osteogenesis imperfecta).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2, 4.4, and 4.8 • PL Section 2 Additional risk minimization measures: • None

Important potential risk: Fracture healing complications	
Evidence for linking the risk to the medicine	This is a theoretical risk based on the potential mechanism of action.
Risk factors and risk groups	General risk factors for fracture healing complications are thought to include older age, diabetes, use of medications such as non-steroidal anti-inflammatory drugs and corticosteroids, smoking, excessive alcohol use, and poor nutrition (Hernandez et al, *Acta Orthopaedica*, 2012;83[6]:653-660; Gaston and Simpson, *J Bone Joint Surg [Br]*, 2007;89-B:1553-1560).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 5.3 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Postmarketing observational Study 20090522 See Section II.C of this summary for an overview of the postauthorization development plan

Important potential risk: Infection	
Evidence for linking the risk to the medicine	This is considered a potential risk based on theoretical concerns which has not been substantiated in the extensive clinical study program or in the postmarketing experience.
Risk factors and risk groups	Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, HIV/AIDS, immunosuppressant drugs (eg, corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.8 • PL Section 4 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Postmarketing observational Study 20090522 See Section II.C of this summary for an overview of the postauthorization development plan

Important potential risk: Cardiovascular events	
Evidence for linking the risk to the medicine	This is a theoretical risk based on epidemiological data demonstrating elevated osteoprotegerin in patients with cardiovascular disease.
Risk factors and risk groups	The denosumab development program comprises studies of older subject populations (eg, osteoporosis, cancer) that are likely to have a higher incidence of pre-existing cardiovascular conditions and, thus, a higher incidence of cardiovascular toxicities than that of the general population (Schulz et al, *J Clin Endocrinol Metab*, 2004;89:4246-4253; Hak et al, *Arterioscler Thromb Vasc Biol*, 2000;20:1926-1931). Risk factors for atherosclerosis include age, sex, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes, and concomitant medications, including antipsychotic agents and COX-2 inhibitors (Murphy and Dargie, *Drug Safety*, 2007;30[9]:783-804; Smith et al, *Circulation*, 2004;109[21]:2613-2616).
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None

Important potential risk: Malignancy	
Evidence for linking the risk to the medicine	This is considered a potential risk based on theoretical concerns and has not been substantiated in the extensive clinical study program or in the postmarketing experience.
Risk factors and risk groups	General factors for risk of malignancy include advancing age, diet, cigarette smoking, excessive ethanol consumption, and numerous environmental toxins. In addition, cancer populations are at increased risk for a second primary malignancy because of their existing malignancy, possible genetic predisposition, and exposure to chemotherapy and radiation treatment (Anand et al, *Pharm Res.* 2008; 25[9]:209-72116; World Health Organization, Global Status Report on Noncommunicable Diseases 2010, http://www.who.int).
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Postmarketing observational Study 20090522 See Section II.C of this summary for an overview of the postauthorization development plan

II.C. Postauthorization Development Plan

II.C.1. Studies Which Are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Prolia.

II.C.2 Other Studies in Postauthorization Development Plan

Study Short Name	Purpose of the Study
20090522 Postmarketing observational study Denosumab global safety assessment among women with postmenopausal osteoporosis (PMO), men with osteoporosis, and men and women who receive Prolia with glucocorticoid exposure in multiple observational databases.	Rationale: A favorable benefit-risk profile of denosumab 60 mg every 6 months (Prolia®) for the treatment of PMO and bone loss associated with hormone ablation in men with prostate cancer was characterized in the original marketing application, which was approved by EMA on 26 May 2010. Amgen also committed to conduct a long-term observational study in administrative databases to prospectively evaluate the incidence of adverse events of special interest (AESI) in postmenopausal women administered Prolia (denosumab). Additional target populations have been added for use of denosumab in men with osteoporosis, and in men and women who receive Prolia with glucocorticoid-induced osteoporosis. Objectives: • Determine incidence rates of AESI in women with PMO exposed to denosumab, women with PMO exposed to bisphosphonates, and among all women with PMO • Describe characteristics, clinical features, and AESI risk factors in women with PMO exposed to denosumab, women with PMO exposed to bisphosphonates, and all women with PMO • Compare the incidence of the AESI in women with PMO exposed to denosumab to that in women with PMO exposed to bisphosphonates • Describe incidence rates of AESI in postmenopausal women • Describe denosumab utilization patterns in subjects who receive denosumab therapy for treatment of PMO • Describe Prolia utilization patterns in subjects who receive Prolia therapy for unapproved indications (indication, dosage, frequency) • In men with osteoporosis treated with denosumab, describe subject characteristics, clinical features, AESI risk factors, subject follow-up, incidence rates of AESI, and denosumab utilization patterns (United States [US] Medicare and Optum Research Database)

Study Short Name	Purpose of the Study
20090522 (Continued)	• In men and women who receive Prolia with glucocorticoid exposure, describe subject characteristics, clinical features, AESI risk factors, subject follow-up, incidence rates of AESI, and denosumab utilization patterns (US Medicare and Optum Research Database) Safety concerns addressed: Hypocalcemia, osteonecrosis of the jaw, atypical femoral fracture, fracture healing complications, infection, hypersensitivity reactions, malignancy.

PART VII: ANNEXES

Table of Contents

Annex 4. Specific Adverse Drug Reaction Follow-up Forms

Table of Contents

Follow-up Form Title	Version Number	Date of Follow-up Version
Hypocalcemia	-	17 April 2014
Infection	-	01 September 2013
Osteonecrosis of the jaw	-	20 November 2015
Postmarketing reports of potential atypical fracture	-	01 November 2015
Fracture healing	-	17 July 2014
Malignancy	-	June 2010
Hypersensitivity	-	05 May 2014

DENOSUMAB Core Questionnaire
Hypocalcemia

AER # | Page 353

This form is subject to applicable laws governing the protection of personal information. The information provided on this form may be transferred and processed outside of the country in which it is collected. Amgen does not wish to receive information through which a patient can be identified therefore please do not provide any information other than the specific information required by this form. This prohibition includes, for example, name, address, telephone number and government issued identifier.

PATIENT / CASE ADMINISTRATIVE INFORMATION (Please indicate dates as DD/MM/YYYY)

Patient Identifier | Patient Initials | Date of Event Onset | Date of This Report

Gender: ☐ Male ☐ Female Weight: _____ lb _____ kg

Age at time of event: _____

Event Reported Term

Study No.

☐ Clinical Trial
☐ Post-marketing

Safety Database No.

DENOSUMAB ADMINISTRATION / INFORMATION (Please indicate dates as DD/MM/YYYY)

Denosumab Indication

☐ Postmenopausal osteoporosis

☐ Bone loss from hormone ablation therapy

Please specify diagnosis _____

☐ Advanced cancer with bone metastasis

Please specify cancer _____

☐ Other

Please specify _____

☐ Don't know

Denosumab Dose

☐ 60 mg SC every 6 months ☐ 120 mg SC every 4 weeks

☐ Other Please specify _____

☐ Don't know

Denosumab Exposure

Denosumab first administered (date) _____

Last denosumab dose before event (date)

☐ Doses of denosumab were skipped ☐ Yes ☐ No ☐ Unknown

If yes, please specify _____

☐ Doses of denosumab given after event began ☐ Yes ☐ No ☐ Unknown

If yes, date of first dose following start of event _____

SIGNS AND SYMPTOMS (Check all that apply)

☐ Numbness
(Specify if involving digits and/or peri-oral region) _____

☐ Convulsions ☐ Muscle twitching

☐ Muscle cramping ☐ Paresthesia

☐ Syncope ☐ Tetany

☐ None ☐ Other _____

DIAGNOSIS (Check all that apply)

Serum calcium at time of event: _____ mg/dL ☐ Unknown

Please provide serum albumin result _____

Serum albumin at the time of event < 4.0 g/dL?
☐ Yes ☐ No ☐ Unknown

If yes, what were the ionized calcium levels? _____ mmol/dL

Serum creatinine at time of event was > 2.0 X times upper limit of normal?
(Please provide result) _____ ☐ Yes ☐ No ☐ Unknown

Hypocalcemia-induced EKG changes (QT prolongation)?
☐ Yes ☐ No ☐ Unknown

TREATMENT

Treated only as an outpatient? ☐ Yes ☐ No

If yes, route of calcium replacement: ☐ IV ☐ Oral ☐ Unknown

Treated in the ER? ☐ Yes ☐ No

If yes, route of calcium replacement: ☐ IV ☐ Oral ☐ Unknown

Treatment included general hospital admission for calcium replacement?
☐ Yes ☐ No ☐ Unknown

If yes, route of calcium replacement: ☐ IV ☐ Oral ☐ Unknown

Treatment included ICU admission? ☐ Yes ☐ No ☐ Unknown

If yes, route of calcium replacement: ☐ IV ☐ Oral ☐ Unknown

Overall length of hospital stay:

☐ ≤ 1 day ☐ > 1 day ☐ ≤ 7 days ☐ > 7 days

Anti-arrhythmic medications? ☐ Yes ☐ No ☐ Unknown

If yes, please provide the details such as names and dates of treatment

Anti-arrhythmic medications _____

Other treatment? ☐ Yes ☐ No ☐ Unknown

If yes, specify: _____

Amgen
Office Fax:

REPORTER Name:

Address:

City: State/ Province:

Country: Postal Code:

Email:

Phone: (include country code)

Signature _____

Title _____ **Date** _____

CONTINUED ON NEXT PAGE

AMGEN®

DENOSUMAB Core Questionnaire Hypocalcemia

AER #		Page 354

PATIENT / CASE ADMINISTRATIVE INFORMATION (Please indicate all dates as DD/MM/YYYY)

Patient Identifier	Patient Initials	Safety Database No.

RISK FACTORS (Check all that apply)

Medical History Risk Factors

Does the patient have any of the following risk factors: ☐ YES ☐ NO

If yes, please provide dates and details:

☐ Acute pancreatitis	☐ History of chronic renal disease	
☐ History of parathyroid disease	☐ History of hypoalbuminemia	
☐ History of malignancy (please specify)	☐ Hypoproteinemia	
☐ Hyperphosphatemia	☐ Magnesium deficiency	
☐ Recent surgery	☐ Sepsis	

☐ Vitamin D deficiency (if patient has a history of vitamin D deficiency, were the vitamin D levels normal at the time of event? Please provide the vitamin D levels at the time of the hypocalcemia event.

☐ Prior hypocalcemia event (before denosumab treatment)
Please provide dates and details of prior hypocalcemia event

Medication Risk Factors

Antineoplastic agents? (Check which apply): ☐ cisplatin ☐ cytosine arabinoside ☐ Other _____ ☐ None

Antimicrobials? (Check which apply): ☐ pentamidine ☐ ketoconazole ☐ Other _____ ☐ None

Concomitant Medications

Taking vitamin D supplement? ☐ Yes ☐ No ☐ Unknown (Please provide dose and dates)

Taking calcium supplement? ☐ Yes ☐ No ☐ Unknown (Please provide dose and dates)

Other concomitant medications _____

Hypocalcemic Event Resolved ☐ Yes ☐ No ☐ Unknown
If yes, what date? (DD/MM/YYYY) _____

REPORTER Name:
Address:
City: State/ Province:
Country: Postal Code:
Email:
Phone: (include country code)
Signature _____
Title _____ **Date** _____

Amgen
Office Fax:

AMGEN

DENOSUMAB Core Questionnaire Infection

AER #

PATIENT / CASE ADMINISTRATIVE INFORMATION (Please indicate dates as DD/MM/YYYY)

Patient Identifier | Patient Initials | Date of Event Onset | Date of This Report

Gender: ☐ Male ☐ Female Weight: ___ lb ___ kg Age at time of event: ___

Event Reported Term | Safety Database No.

Study No. ☐ Clinical Trial ☐ Post-marketing

DENOSUMAB ADMINISTRATION / INFORMATION (Please indicate dates as DD/MM/YYYY)

Denosumab Indication

☐ Postmenopausal osteoporosis

☐ Bone loss from hormone ablation therapy

Please specify diagnosis ___

☐ Advanced cancer with bone metastasis

Please specify cancer ___

☐ Other (please specify) ___

☐ Don't know

Denosumab Dose: ☐ 60 mg SC every 6 mos ☐ 120 mg SC every 4 wks

☐ Other (please specify) ___ ☐ Don't know

Denosumab Exposure: Denosumab first administered (date) ___

Last denosumab dose before event (date) ___

☐ Doses of denosumab were skipped ☐ Yes ☐ No ☐ Unknown

If yes, please specify ___

☐ Doses of denosumab given after event began ☐ Yes ☐ No ☐ Unknown

If yes, date of first dose following start of event ___

SIGNS AND SYMPTOMS (Check all that apply, provide dates of onset, resolution, if available)

☐ Fever___
☐ Cough ___
☐ Swelling ___
Location ___
☐ Shortness of breath
___

☐ Pain ___
Location ___
☐ Rash ___
Location ___
☐ Prolonged fatigue ___
☐ Diarrhea ___

☐ Discharge ___
Location ___
Description ___
☐ Chills ___
☐ Night sweats ___
☐ Other___

☐ Organ system affected:
☐ Cardiac
☐ Ear/nose
☐ Throat
☐ Gastrointestinal
☐ Respiratory
☐ Musculoskeletal (including joints)
☐ Nervous (cerebrospinal fluid)
☐ Skin Location ___
☐ Kidney/genito-urinary
☐ Systemic (bacteremia and/or sepsis)
☐ Other ___

EVALUATIONS, DIAGNOSIS & LABORATORY MEASURES (Please attach copy of report)

Diagnostic	Results/Units	Reference Range/Units	Date	Report Attached Y	N	Diagnostic	Results/Units	Reference Range/Units	Date	Report Attached Y	N

CONTINUED ON NEXT PAGE

PATIENT / CASE ADMINISTRATIVE INFORMATION (Please indicate all dates as DD/MM/YYYY)

Patient Identifier	Patient Initials	Safety Database No.

REPORTS/RELEVANT FINDINGS (Please provide dates, baseline information and indicate attachments if available)

CHECK WHICH INFECTION APPLIES

- ☐ Cardiac infections
  - ☐ Endocarditis _____
  - ☐ Pericarditis (purulent; tuberculous) _____
  - ☐ Other, please specify: _____
- ☐ Ear and labyrinth infections
  - ☐ Otitis media _____
  - ☐ Otitis externa _____
  - ☐ Other, please specify: _____
- ☐ Gastrointestinal/abdominal infections
  - ☐ Colitis _____
  - ☐ Diverticulitis _____
  - ☐ Appendicitis _____
  - ☐ Abdominal sepsis (including peritonitis) _____
  - ☐ Hepatic abscess _____
  - ☐ Hepatitis B _____
  - ☐ Hepatitis C _____
  - ☐ Other, please specify: _____
- ☐ Musculoskeletal and connective tissue infections
  - ☐ Osteomyelitis _____
  - ☐ Septic arthritis _____
  - ☐ Other, please specify: _____
- ☐ Nervous system infections
  - ☐ Meningitis _____
  - ☐ Encephalitis _____
  - ☐ Other, please specify: _____
- ☐ Respiratory tract infections
  - ☐ Pneumonia _____
  - ☐ Pulmonary TB _____
  - ☐ Lung abscess _____
  - ☐ Legionnella pneumonia _____
  - ☐ Mycoplasma pneumonia _____
  - ☐ Other, please specify: _____
- ☐ Kidney and genito-urinary tract infections
  - ☐ Cystitis _____
  - ☐ Pyelonephritis _____
  - ☐ Urinary tract infection _____
  - ☐ Other, please specify: _____
- ☐ Systemic infections
  - ☐ Bacteremia _____
  - ☐ Sepsis _____
  - ☐ Toxic shock syndrome _____
  - ☐ Other, please specify: _____

_____

- ☐ Wound and skin infections
  - ☐ Cellulitis _____
  - ☐ Erysipelas _____
  - ☐ Necrotizing fasciitis _____
  - ☐ Abscess _____
  - ☐ Other skin infections, please specify: _____
- ☐ Opportunistic infections
  - ☐ Aspergillus (invasive forms only) _____
  - ☐ Blastomycosis pulmonary or extra-pulmonary infections _____
  - ☐ Candidiasis systemic _____
  - ☐ Coccidioidemycosis secondary/systemic _____
  - ☐ Cryptococcal infection – pulmonary and non-pulmonary _____
  - ☐ Cytomegalovirus – include systemic site _____
  - ☐ Herpes simplex (meningitis or encephaltitis) _____
  - ☐ Herpes zoster (only systemic or disseminated: involving 2 or more dermatomes) _____
  - ☐ Histoplasma infections - chronic disseminated or severe acute _____
  - ☐ Mucormycosis (=zygomycosis) including infections due to Rhizopus, Mucor and Absidia of lung, genito-urinary tract, kidney, GIT, skin _____
  - ☐ Mycobacterium tuberculosis _____
  - ☐ Non-tuberculosis mycobacterium _____
  - ☐ Nocardia infection – of brain, lungs, kidney, skin _____
  - ☐ Paracoccidioides infections of lungs, skin other _____
  - ☐ Pneumocystis carinii pneumonia _____
  - ☐ Sporotrichosis – disseminated infections _____
  - ☐ Toxoplasmosis encephalitis or disseminated _____
  - ☐ Other opportunistic infections, please specify: _____
- ☐ Other infections, please specify: _____

_____

- ☐ Parasitic evaluation (ova, etc.) _____

REPORTER

Name:

Address:

City: State/ Province:

Country: Postal Code:

Email:

Phone: (include country code)

Signature _____

Title _____ **Date** _____

Amgen
Office Fax:

CONTINUED ON NEXT PAGE

PATIENT / CASE ADMINISTRATIVE INFORMATION (Please indicate all dates as DD/MM/YYYY)

Patient Identifier | Patient Initials | Safety Database No.

REPORTS/RELEVANT FINDINGS (Continued) (Please provide dates, baseline information and indicate attachments if available)

DIAGNOSTICS

☐ Cultures done ☐ No ☐ Yes ☐ Unknown
If yes, check which apply:
☐ Blood culture _____
☐ Culture positive ☐ No ☐ Yes ☐ Unknown
If yes, which ☐ Bacterial ☐ Fungal ☐ Viral
☐ Pathogen identified: _____
☐ Urine culture _____
☐ Culture positive ☐ No ☐ Yes ☐ Unknown
If yes, which ☐ Bacterial ☐ Fungal ☐ Viral
☐ Pathogen identified: _____
☐ Sputum culture _____
☐ Culture positive ☐ No ☐ Yes ☐ Unknown
If yes, which ☐ Bacterial ☐ Fungal ☐ Viral
☐ Pathogen identified: _____
☐ Synovial culture _____
☐ Culture positive ☐ No ☐ Yes ☐ Unknown
If yes, which ☐ Bacterial ☐ Fungal ☐ Viral
☐ Pathogen identified: _____

☐ Cerebrospinal fluid culture
☐ Culture positive ☐ No ☐ Yes ☐ Unknown
If yes, which ☐ Bacterial ☐ Fungal ☐ Viral
☐ Pathogen identified: _____
☐ Tissue culture _____
If yes, specify: ☐ Brain ☐ Lung ☐ Liver
☐ Kidney ☐ Skin ☐ Bone ☐ Other
☐ Culture positive ☐ No ☐ Yes ☐ Unknown
If yes, which ☐ Bacterial ☐ Fungal ☐ Viral
☐ Pathogen identified: _____
☐ Catheter Tip/Line _____
☐ Culture positive ☐ No ☐ Yes ☐ Unknown
If yes, which ☐ Bacterial ☐ Fungal ☐ Viral
☐ Pathogen identified: _____
☐ PPD placement ☐ No ☐ Yes ☐ Unknown
If yes, PPD positive ☐ No ☐ Yes ☐ Unknown
_____
_____

☐ Parasitic evaluation (ova, etc.) _____
☐ X-ray ☐ No ☐ Yes ☐ Unknown _____
☐ MRI ☐ No ☐ Yes ☐ Unknown _____
☐ CT scan ☐ No ☐ Yes ☐ Unknown
_____
☐ Bone scan ☐ No ☐ Yes ☐ Unknown
_____
☐ Other _____
☐ Rapid test _____
☐ Serum titres _____
☐ Hospital discharge report _____
_____
☐ Other consult report _____
_____
☐ Provide final diagnosis and treatment, if available (please specify) _____
_____
☐ Outcome and resolution date _____

TREATMENT

☐ ER antibiotics ☐ No ☐ Yes ☐ Unknown
If yes, route
☐ IV ☐ Oral ☐ SC ☐ Both oral and IV
☐ Required hospital admission
☐ No ☐ Yes ☐ Unknown
☐ ICU admission ☐ No ☐ Yes ☐ Unknown
If yes, reason for ICU admission _____

Overall length of hospital stay
☐ < 1 day ☐ > 1 day or < 7 days ☐ > 7 days
_____
☐ In-hospital antibiotics
☐ No ☐ Yes ☐ Unknown
☐ If yes, route of administration
☐ IV ☐ Oral ☐ Both oral and IV

☐ Other in-hospital treatment
☐ Antivirals ☐ No ☐ Yes ☐ Unknown
If yes, route of administration ☐ IV ☐ Oral
☐ Antifungals ☐ No ☐ Yes ☐ Unknown
If yes, route of administration ☐ IV ☐ Oral
☐ Surgery ☐ No ☐ Yes ☐ Unknown
☐ Hyperbaric oxygen ☐ No ☐ Yes ☐ Unknown

PATIENT HISTORY/RISK FACTORS (Please provide history, dates, severity of reaction and intervention)

Please specify any post operative complications, chronic disease or infection, etc.
☐ Chronic lung disease _____
☐ Hepatitis _____
☐ Chronic kidney disease _____
☐ Liver disease _____
☐ Congenital infections/malformations _____
☐ Osteomyelitis _____
☐ HIV _____
☐ Diabetes mellitus _____
☐ Cancer (specify) _____
☐ Recent wounds/infections _____
☐ Immunosuppression _____
☐ Known exposure to TNF inhibitors _____
☐ Chemotherapy _____
☐ Malnutrition/failure to thrive _____
☐ Exposure to infectious agents _____
☐ Personal contact ____ ☐ Body fluids ____
☐ Share personal items (razor, needles, etc) ____
☐ Potentially contaminated food/liquid ____

Exposure to infectious agents (continued)
☐ Hospital acquired _____
☐ Other _____
☐ Steroid exposure _____
☐ Insect/tick bite _____
☐ Drug or IV drug abuse: Type _____
Amount _____
Frequency _____
☐ Alcohol/tobacco use: Type _____
Amount _____
Frequency _____
☐ Indwelling catheters _____
_____
_____
☐ Recent skin injury
_____
_____
☐ Recent travel (specify)
_____
_____

☐ Exposure to animals/zoonotic diseases (exposure to infected animal) _____
☐ Unprotected sex _____
☐ Immobility _____
☐ Indwelling catheters _____
☐ Nursing home resident _____
☐ Occupational exposure _____
☐ Ostomy _____
☐ Post influenza _____
☐ Surgery < 30 days _____
☐ TB exposure _____
☐ Other history/risk factors _____

Amgen
Office Fax:

REPORTER Name:
Address:
City: State/ Province:
Country: Postal Code:
Email:
Phone: (include country code)
Signature _____
Title _____ **Date** _____

DENOSUMAB Core Questionnaire
Osteonecrosis of the Jaw

AER # | Page 358

PATIENT / CASE ADMINISTRATIVE INFORMATION (Please indicate dates as DD/MM/YYYY)

Patient Identifier | Patient Initials | Date of Event Onset | Date of This Report

Gender: ☐ Male ☐ Female Weight: _____ lb _____ kg

Age at time of event: _____

Event Reported Term

Study No.

☐ Clinical Trial
☐ Post-marketing

Safety Database No.

DENOSUMAB ADMINISTRATION / INFORMATION (Please indicate dates as DD/MM/YYYY)

Denosumab Indication

☐ Postmenopausal osteoporosis
☐ Bone loss from hormone ablation therapy
Please specify diagnosis _____
☐ Advanced cancer with bone metastasis
Please specify cancer _____
☐ Other
Please specify _____
☐ Don't know

Denosumab Dose

☐ 60 mg SC every 6 months ☐ 120 mg SC every 4 weeks
☐ Other Please specify _____
☐ Don't know

Denosumab Exposure

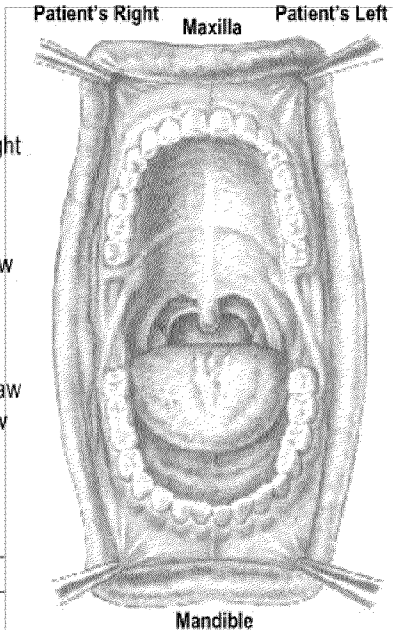
Denosumab first administered (date) _____
Last denosumab dose before event (date) _____
☐ Doses of denosumab were skipped ☐ No ☐ Yes ☐ Unknown
If yes, please specify _____
☐ Doses of denosumab given after event began ☐ No ☐ Yes ☐ Unknown
If yes, date of first dose following start of event _____

EVIDENCE OF EXPOSED BONE (Please indicate dates as DD/MM/YYYY)

Visible evidence of exposed bone, or bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial region:
☐ No ☐ Yes ☐ Unknown; Please describe _____

Date exposed bone was first visualized/probed: _____
Exposed bone or probed bone that has persisted for more than eight weeks:
☐ No ☐ Yes ☐ Unknown _____
Prior history of radiation therapy to jaw:
☐ No ☐ Yes ☐ Unknown _____
Prior history of metastatic disease to jaw:
☐ No ☐ Yes ☐ Unknown
Describe: _____

Please indicate the location of involved area(s) on the diagram at right (mark site(s) clearly with 'X').



Please describe location(s):
☐ Right maxilla, teeth and lateral jaw
☐ Left maxilla, teeth and lateral jaw
☐ Right maxilla, medial jaw
☐ Left maxilla, medial jaw
☐ Right mandible teeth and lateral jaw
☐ Left mandible teeth and lateral jaw
☐ Right mandible, medial jaw
☐ Left mandible, medial jaw
☐ Maxilla hard palate
☐ Other (specify) _____

Oral Findings

Evidence of infection: ☐ No ☐ Yes ☐ Unknown
Please describe _____

Exposed bone at the site of extraction: ☐ No ☐ Yes ☐ Unknown

Complete coverage of involved area(s) by mucosa: ☐ No ☐ Yes ☐ Unknown
If yes, date of complete mucosal coverage _____

CLINICAL SYMPTOMS (Please indicate dates as DD/MM/YYYY)

Date of first clinical signs/symptoms in the mouth (eg. infection, pain, inflammation): _____
Please describe the clinical signs/symptoms/location:

REPORTER Name:
Address:
City: State/ Province:
Country: Postal Code:
Email:
Phone: (include country code)
Signature _____
Title _____ **Date** _____

Amgen
Office Fax:

CONTINUED ON NEXT PAGE

PATIENT / CASE ADMINISTRATIVE INFORMATION (Please indicate all dates as DD/MM/YYYY)

Patient Identifier | Patient Initials | Safety Database No.

CONSULTATIONS (Please indicate all dates as DD/MM/YYYY)

Dental / oral surgery / stomatology consultations ☐ No ☐ Yes ☐ Unknown If yes, please give date of examination _____
Please provide any consult reports, radiographs, pictures if available _____

TREATMENT INFORMATION (Please indicate what treatments were administered and indicate dates as DD/MM/YYYY)

Antibiotics ☐ No ☐ Yes ☐ Unknown If yes, agent(s)/route/dose _____ Start date _____ Stop date _____
Please describe outcomes of treatment _____
Oral rinses ☐ No ☐ Yes ☐ Unknown If yes, agent(s)/dose _____
Please describe outcomes of treatment _____
Oral surgery ☐ No ☐ Yes ☐ Unknown If yes, type of surgery _____
Start date _____ Stop date _____
Please describe outcomes of treatment _____
Hospitalizations ☐ No ☐ Yes ☐ Unknown If yes, reason for hospitalization _____
Hospitalization begin date _____ Hospitalization end date _____
Please describe outcomes of treatment _____

DENTAL HISTORY (Please indicate all dates as DD/MM/YYYY)

History of poor oral hygiene ☐ No ☐ Yes ☐ Unknown _____
Dental extraction recently ☐ No ☐ Yes ☐ Unknown If yes, date of procedure _____
Dental surgery recently ☐ No ☐ Yes ☐ Unknown If yes, date of procedure _____
Periodontal disease including gingival bleeding, calculus, etc. ☐ No ☐ Yes ☐ Unknown Start date _____ Stop date _____
Draining fistula in affected area ☐ No ☐ Yes ☐ Unknown Start date _____ Stop date _____
Dental abscess in affected area ☐ No ☐ Yes ☐ Unknown Start date _____ Stop date _____
Osteomyelitis in affected area ☐ No ☐ Yes ☐ Unknown Start date _____ Stop date _____
Root-canal treatment near affected area ☐ No ☐ Yes ☐ Unknown If yes, date of treatment _____
Dental treatment, surgery or tooth extraction to the involved area within the last 4–6 months PRIOR to the onset of the oral lesion ☐ No ☐ Yes ☐ Unknown
History of dentures / dental appliance / implant ☐ No ☐ Yes ☐ Unknown If yes, please specify ☐ Upper ☐ Lower
Area of lesion at or near a contact point ☐ No ☐ Yes ☐ Unknown

MEDICATIONS (Please indicate all dates as DD/MM/YYYY)

PO bisphosphonate ☐ No ☐ Yes ☐ Unknown
If yes, agent(s)/dose _____
Start date _____ Stop date _____
IV bisphosphonate ☐ No ☐ Yes ☐ Unknown If yes, agent(s)/dose _____
Start date _____ Stop date _____
Glucocorticoid use within the past 12 months ☐ No ☐ Yes ☐ Unknown If yes, agent(s)/dose _____
Start date _____ Stop date _____
Immunosuppressant use within the past 12 months ☐ No ☐ Yes ☐ Unknown If yes, agent(s)/dose _____
Start date _____ Stop date _____
Chemotherapy within the past 12 months ☐ No ☐ Yes ☐ Unknown If yes, agent(s)/dose _____
Start date _____ Stop date _____
Anti-angiogenic agents (e.g. bevacizumab) within the past 12 months ☐ No ☐ Yes ☐ Unknown If yes, agent(s)/dose _____
Start date _____ Stop date _____

OTHER HISTORY (Please indicate all dates as DD/MM/YYYY)

Current smoker ☐ No ☐ Yes ☐ Unknown
If yes, estimated number of pack-years _____
If past smoker, stop date _____
Alcohol consumption ☐ No ☐ Yes ☐ Unknown
If yes, estimated of drinks per week _____
Diabetes ☐ No ☐ Yes ☐ Unknown If yes, ☐ Type I ☐ Type II

Amgen
Office Fax:

Patient Reminder Card Status (For EU Patients)

Received a patient reminder card prior to the ONJ event:
☐ Yes ☐ No ☐ Unknown

CONTINUED FROM PREVIOUS PAGE

AMGEN

DENOSUMAB Core Questionnaire
POSTMARKETING REPORTS OF POTENTIAL ATYPICAL FRACTURE
(low energy, subtrochanteric/femoral shaft fractures)

AER # |

PATIENT / CASE ADMINISTRATIVE INFORMATION (Please indicate dates as DD/MM/YYYY)

Patient Identifier

Patient Initials

Date of Event Onset

Date of This Report

Gender: ☐ Male ☐ Female Weight: _____ lb _____ kg

Age at time of event: _____

Study Number (If applicable)

Event

DENOSUMAB ADMINISTRATION / INFORMATION (Please indicate dates as DD/MM/YYYY)

Denosumab Indication:

☐ Postmenopausal osteoporosis

☐ Bone loss from hormone ablation therapy
Please specify diagnosis _____

☐ Advanced cancer with bone metastasis
Please specify cancer _____

☐ Other (please specify) _____

☐ Don't know _____

Denosumab Dose: ☐ 60 mg SC every 6 months ☐ 120 mg SC every 4 weeks
☐ Other (please specify) _____ ☐ Don't know

Denosumab Exposure:

Denosumab first administered (date) _____

Last denosumab dose before event (date) _____

Doses of denosumab were skipped ☐ Yes ☐ No ☐ Unknown
If yes, please specify _____

Doses of denosumab given after event began ☐ Yes ☐ No ☐ Unknown
If yes, date of first dose following start of event _____

DIAGNOSIS (Check all that apply)

Location of fracture:

☐ Femur neck

☐ Femur distal

☐ Femur midshaft

☐ Femur intertrochanter

☐ Femur subtrochanter

☐ Other location (specify): _____

Diagnostic imaging used to confirm fracture:
☐ X-ray ☐ CT scan ☐ MRI

Date of imaging at time of femur fracture (DD/MM/YYYY): _____

☐ **Please attach a copy of applicable radiology report(s).**

Was this a pathological fracture associated with bone tumor or miscellaneous bone diseases (e.g. Paget's disease, fibrous dysplasia)?
☐ Yes ☐ No ☐ Unknown

Type of fracture:
☐ Transverse
☐ Oblique
☐ Spiral
☐ Not reported

Fracture radiology report includes:

Simple transverse or oblique (30°) fracture with beaking of the cortex:
☐ Yes ☐ No ☐ Not reported

Diffuse cortical thickening of the proximal femoral shaft:
☐ Yes ☐ No ☐ Not reported

Type of trauma reported at time of fracture:

☐ No trauma

☐ Fall from standing height or less

☐ Fall on stairs, steps or curbs

☐ Fall from the height of stool, chair, first rung on a ladder or equivalent (about 20 inches)

☐ Minimal trauma other than a fall

☐ Fall from higher than the height of a stool, chair, first rung on a ladder or equivalent (> 20 inches)

☐ Severe trauma other than a fall (e.g., car accident)

☐ Unknown type of trauma

Early symptom of pain over fracture site:

☐ Pain at site at rest

☐ Pain at site with weight bearing

☐ None

Fracture healed (union) within 6 months ☐ Yes ☐ No ☐ Unknown

If yes:

☐ Date of fracture union (DD/MM/YYYY): _____

☐ Patient able to walk without assistance: ☐ Yes ☐ No ☐ Unknown

☐ Fracture union confirmed through imaging: ☐ Yes ☐ No ☐ Unknown
If yes, check all diagnostic imaging that applies: ☐ X-ray ☐ CT scan ☐ MRI

CONTINUED ON NEXT PAGE (PAGE 1 OF 2)

AMGEN

DENOSUMAB Core Questionnaire

POSTMARKETING REPORTS OF POTENTIAL ATYPICAL FRACTURE

(low energy, subtrochanteric/femoral shaft fractures)

AER #		Page 361

PATIENT / CASE ADMINISTRATIVE INFORMATION (Please indicate all dates as DD/MM/YYYY)

Patient Identifier	Patient Initials	Date of This Report

TREATMENT (Please provide dates and indicate attachments if available)

Methods to reduce and set fracture:

☐ Non-surgical reduction _____

☐ Casting _____

☐ Surgery _____

☐ Revision surgery (2nd surgery) _____

☐ Other _____

_____

☐ Unknown _____

_____

MEDICAL HISTORY/RISK FACTORS (Check all that apply, provide dates and attach relevant reports)

General:

☐ History or current corticosteroid use

☐ Affected hip with prior surgical pinning

☐ Affected hip with prior hip replacement

Cancer:

Evidence of any metastases: ☐ Yes ☐ No ☐ Unknown

If yes, did metastasis involve bone? ☐ Yes ☐ No ☐ Unknown

Metastasis in femur where fracture occurred? ☐ Yes ☐ No ☐ Unknown

Prior osteoporosis therapy:

☐ Estrogen

☐ Selective estrogen receptor modulator (SERM)

☐ Bisphosphonate (please indicate)

☐ Intravenous ☐ Oral

If yes, how long has therapy been received? (months, years) _____

☐ Parathyroid hormone

Past medical and surgical history: _____

_____

_____

_____

Medication history (include dose, frequency, and dates of treatment): _____

_____

_____

_____

Copies of records/consults/radiology report attached? ☐ Yes ☐ No

_____

_____

_____

Amgen
Office Fax:

REPORTER

Name:

Address:

City:

Country:

Email:

Phone: (include country code)

State/
Province:

Postal Code:

Signature _____

Title _____ **Date** _____

AMGEN

DENOSUMAB Core Questionnaire FRACTURE HEALING

AER #

PATIENT / CASE ADMINISTRATIVE INFORMATION (Please indicate dates as DD/MM/YYYY)

Patient Identifier

Patient Initials

Date of Event Onset

Date of This Report

Gender: ☐ Male ☐ Female Weight: _____ lb _____ kg

Age at time of event: _____

Event Reported Term

Study No.

☐ Clinical Trial
☐ Post-marketing

Safety Database No.

DENOSUMAB ADMINISTRATION / INFORMATION (Please indicate dates as DD/MM/YYYY)

Denosumab Indication:

☐ Postmenopausal osteoporosis
☐ Bone loss from hormone ablation therapy
Please specify diagnosis _____
☐ Advanced cancer with bone metastasis
Please specify cancer _____
☐ Other (please specify) _____
☐ Don't know

Denosumab Dose: ☐ 60 mg SC every 6 months ☐ 120 mg SC every 4 weeks
☐ Other (please specify) _____ ☐ Don't know

Denosumab Exposure:

Denosumab first administered (date) _____ (study #) _____
Last denosumab dose before event (date) _____
Doses of denosumab were skipped ☐ Yes ☐ No ☐ Unknown
If yes, please specify _____
Doses of denosumab given after event began ☐ Yes ☐ No ☐ Unknown
If yes, date of first dose following start of event _____

DIAGNOSIS (Check all that apply, please indicate dates as DD/MM/YYYY)

Date of fracture: _____ Date of fracture delayed healing: _____ Date of fracture non-healing:

☐ **Fracture to upper body (i.e., above waist)**

Specify location (check all that apply):

☐ Cervical spine
☐ Clavicle
☐ Hand/metacarpal/phalange
☐ Head/face/skull
☐ Humerus
☐ Olecranon
☐ Radius
☐ Rib
☐ Scapula
☐ Shoulder
☐ Sternum
☐ Ulna
☐ Wrist/carpal
☐ Other _____

☐ **Fracture to lower body (i.e., below waist)**

Specify location (check all that apply):

☐ Ankle
☐ Femur (please specify location: neck, subtrochanteric, mid shaft, etc)
_____
_____
☐ Foot/tarsal/metatarsal/phalange
☐ Hip
☐ Patella
☐ Pelvis
☐ Tibia
☐ Fibula
☐ Other _____

Type of trauma reported at time of fracture (check one):

☐ Severe trauma (e.g., falling from roof, motor vehicle accident)
☐ Minimal trauma (e.g., falling from standing position or less)
☐ Non-traumatic

Characteristics of fracture (check all that apply):

☐ Comminuted
☐ Compound
☐ Pathologic
☐ Poor alignment
☐ Poor immobilization of segments
☐ Soft tissue injury
☐ Unknown

CONTINUED ON NEXT PAGE

AMGEN®

DENOSUMAB Core Questionnaire FRACTURE HEALING (continued)

AER #

PATIENT / CASE ADMINISTRATIVE INFORMATION (Please indicate all dates as DD/MM/YYYY)

Patient Identifier | Patient Initials | Safety Database No.

TREATMENT (Please provide dates and indicate attachments if available)

Methods to reduce and set fracture (check all that apply):

☐ Casting _____ ☐ Surgery _____

☐ Non-surgical reduction _____ ☐ Traction _____

☐ Revision surgery (2nd surgery) _____ ☐ Other _____

Did the fracture heal (union)? ☐ Yes ☐ No ☐ Unknown

If yes, provide date of union (DD/MM/YYYY): _____

If yes, was healing confirmed through imaging? ☐ Yes ☐ No ☐ Unknown

If yes, what diagnostic imaging (check all that apply): ☐ X-rays ☐ CT scanes ☐ MRI

If yes, is patient able to walk without assistance? ☐ Yes ☐ No ☐ Unknown

MEDICAL HISTORY/RISK FACTORS (Check all that apply, provide dates and attach relevant reports)

☐ Current smoker/tobacco use _____

☐ History or current corticosteroid use _____

☐ Prior fracture history _____

☐ Diabetes _____

Amgen
Office Fax:

REPORTER

Name:

Address:

City:

State/ Province:

Postal Code:

Country:

Email:

Phone: (include country code)

Signature _____

Title _____ **Date** _____

Office Patient Identifier _____Patient Initials _____Amgen AER No. _____

Questionnaire for Malignancy Adverse Events

Date of event onset (DD/MM/YYYY): ____/____/_____

Is this a new primary malignancy? Yes ☐ No ☐ Unknown ☐

If no, is this a recurrence of a previous cancer? Yes ☐ No ☐ Unknown ☐

Does patient have history of other malignancy? Yes ☐ No ☐ Unknown ☐

If yes, date of prior cancer (DD/MM/YYYY): ____/____/_____

Tumor stage, if known: _____

Primary site of malignancy: _____

Tumor Stage:

Tumor Size (Check which one applies):

TX ☐ T0 ☐ Tis ☐ T1 ☐ T2 ☐ T3 ☐ T4 ☐

Tumor Grade (Check which one applies):

GX ☐ G1 ☐ G2 ☐ G3 ☐

Localized (no regional involvement/no distant metastasis)? Yes ☐ No ☐

(If yes, skip next 2 questions)

Lymph Node Involvement (Check which one applies):

NX ☐ N1 ☐ N2 ☐ N3 ☐

Metastases (Check which one applies):

MX ☐ M0 ☐ M1 ☐

TREATMENT:

Hospitalized? Yes ☐ No ☐ Unknown ☐

ICU admission? Yes ☐ No ☐ Unknown ☐

Overall length of hospital stay: ≤ 1 day ☐ > 1 day or ≤ 7 days ☐ > 7 days ☐

Surgical treatment? Yes ☐ No ☐ Unknown ☐

Chemotherapy (includes biologics)? Yes ☐ No ☐ Unknown ☐

Hormonal treatment? Yes ☐ No ☐ Unknown ☐

Radiation treatment? Yes ☐ No ☐ Unknown ☐

Bone marrow transplant? Yes ☐ No ☐ Unknown ☐

If yes, autologous ☐ heterologous ☐

Was the malignancy treated with curative intention? Yes ☐ No ☐ Unknown ☐

RISK FACTORS (Check all that apply):

Smoking ☐

Prior Malignancy ☐

Positive Family History (Check all that apply):

Same cancer ☐

Different cancer ☐

Prior therapeutic radiation exposure ☐

Environmental exposure ☐

Specify: _____

AMGEN

DENOSUMAB Core Questionnaire HYPERSENSITIVITY

AER #

PATIENT / CASE ADMINISTRATIVE INFORMATION (Please indicate dates as DD/MM/YYYY)

Patient Identifier

Patient Initials

Date of Event Onset

Date of This Report

Gender: ☐ Male ☐ Female Weight: _____ lb _____ kg

Age at time of event: _____

Event Reported Term

Study No.

☐ Clinical Trial
☐ Post-marketing

Safety Database No.

DENOSUMAB ADMINISTRATION / INFORMATION (Please indicate dates as DD/MM/YYYY)

Denosumab Indication:

☐ Postmenopausal osteoporosis
☐ Bone loss from hormone ablation therapy
Please specify diagnosis _____
☐ Advanced cancer with bone metastasis
Please specify cancer _____
☐ Other (please specify) _____
☐ Don't know _____

Denosumab Dose: ☐ 60 mg SC every 6 months ☐ 120 mg SC every 4 weeks
☐ Other (please specify) _____ ☐ Don't know

Denosumab Exposure:
Denosumab first administered (date) _____ (study #) _____
Last denosumab dose before event (date) _____
☐ Doses of denosumab were skipped ☐ Yes ☐ No ☐ Unknown
If yes, please specify _____
☐ Doses of denosumab given after event began ☐ Yes ☐ No ☐ Unknown
☐ If yes, date of first dose following start of event _____

☐ **Denosumab Antibody Testing Performed:** (provide dates and results) _____
If not performed, do you have interest in antibody testing? ☐ Yes ☐ No _____

SIGNS AND SYMPTOMS (Check all that apply)

☐ Anaphylaxis	☐ Facial edema	☐ Rash	☐ Diarrhea	☐ Tachycardia	☐ Other (specify)
☐ Angioneurotic edema	☐ Hypotension	☐ Shortness of breath	☐ Pruitis	☐ Urticaria	_____
☐ Colic	☐ Laryngeal edema	☐ Stridor	☐ Swelling	☐ Wheezing	_____

EVALUATIONS, DIAGNOSIS & LABORATORY MEASURES (Please indicate and attach copy of report if available)

Diagnostic	Results/Units	Reference Range/ Units	Date	Report Attached Y / N	
Results at BASELINE (prior to Amgen drug)					
CBC with Differential					
WBC					
RBC					
Eosinophils					
Hgb					
Hct					
Platelets					
Other					
Albumin					
Total Protein					
BUN					
Serum Creatinine					
ALT					
AST					
ALP					
Bilirubin					
Calcium					
K+					
Na+					
Phosphorus					
Mg++					
Cl-					
CrCl					

Diagnostic	Results/Units	Reference Range/ Units	Date	Report Attached Y / N	
Results at TIME OF EVENT					
CBC with Differential					
WBC					
RBC					
Eosinophils					
Hgb					
Hct					
Platelets					
Other					
Albumin					
Total Protein					
BUN					
Serum Creatinine					
ALT					
AST					
ALP					
Bilirubin					
Calcium					
K+					
Na+					
Phosphorus					
Mg++					
Cl-					
CrCl					

CONTINUED ON NEXT PAGE

AMGEN

DENOSUMAB Core Questionnaire HYPERSENSITIVITY (continued)

AER #

PATIENT / CASE ADMINISTRATIVE INFORMATION (Please indicate all dates as DD/MM/YYYY)

Patient Identifier | Patient Initials | Safety Database No.

TREATMENT (Please provide dates and indicate attachments if available)

☐ ER corticosteroids

Route: ☐ IV ☐ oral

☐ ER anti-histaminics

Route: ☐ IV only ☐ oral only ☐ both oral and IV

☐ Required hospital admission ☐ Yes ☐ No

Overall length of hospital stay

☐ < 1 day ☐ > 1 day or < 7 days ☐ > 7 days

☐ ICU admission ☐ Yes ☐ No ☐ Unknown

Overall length of hospital stay

☐ < 1 day ☐ > 1 day or < 7 days ☐ > 7 days

☐ In-hospital corticosteroids

Route: ☐ IV only ☐ oral only ☐ both oral and IV

☐ In-hospital anti-histaminics

Route: ☐ IV only ☐ oral only ☐ both oral and IV

☐ Other in-hospital treatment

☐ IV vasopressors ☐ Yes ☐ No ☐ Unknown

☐ Intubation/mechanical ventilation ☐ Yes ☐ No ☐ Unknown

☐ Hospital admissions/discharge report (please attach if available)

_____

_____

_____

_____

_____

_____

_____

Amgen
Office Fax:

CONCOMITANT MEDICATIONS

☐ ACE inhibitors
☐ Allopurinol
☐ Cancer chemotherapy
☐ Dapsone
☐ IV contrast
☐ NSAIDS/aspirin
☐ Penicillamine
☐ Rifampin

☐ Anticonvulsants (check which apply):

- ☐ Phenytoin
- ☐ Carbamazepine
- ☐ Phenobarbital

☐ Antibiotics (check which apply):

- ☐ Beta-lactams including penicillin and cephalosporin
- ☐ Macrolides
- ☐ Sulfonamides
- ☐ Quinolones

☐ Hypersensitivity event resolved ☐ Yes ☐ No ☐ Unknown

If yes, date (DD/MM/YYYY): _____

☐ Final diagnosis or etiology (incl. start date). Please send supporting documents for diagnosis _____

☐ Other consult report (please indicate any attachments) _____

_____

_____

_____

REPORTER Name:

Address:

City: State/ Province:

Country: Postal Code:

Email:

Phone: (include country code)

Signature _____

Title _____ **Date** _____

Annex 6. Details of Proposed Additional Risk Minimization Activities (if applicable)

Approved key messages of the additional risk minimization measures

Patient reminder card:

Patient Reminder Cards for osteonecrosis of the jaw (ONJ) will be distributed to prescribers of Prolia® with background information on the purpose of the patient reminder card and instructions to provide it to patients.

The patient reminder card will remind patients about important safety information that they need to be aware of before and during treatment with denosumab (Prolia®) injections for osteoporosis and bone loss, including:

- the risk of osteonecrosis of the jaw during treatment with Prolia®;
- the need to highlight any problems with their mouth or teeth to their doctors/nurses before starting treatment;
- the need to ensure good oral hygiene during treatment;
- the need to inform their dentist of treatment with Prolia® and to contact their doctor and dentist if problems with the mouth or teeth occur during treatment.

The patient reminder card will be distributed by mail and prescribers will be provided with contact details to request additional copies of the card. Some national plans will include making the patient reminder card available on a website and this approach may be extended in the future.