EUROPEAN UNION RISK MANAGEMENT PLAN

Denosumab (XGEVA®)

Sponsor:	Amgen Europe B.V. Minervum 7061 4817 ZK Breda, Netherlands
Version:	36.0
Date:	11 December 2020
Supersedes:	Version 35.0, dated 28 February 2020

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

RMP version number:	36.0
Data lock point of this RMP:	26 September 2020
Date of final sign-off:	11 December 2020
Rationale for submitting an updated RMP:	Removal of the important potential risks of Infection and Osteonecrosis outside of the jaw including external auditory canal and the missing information of Immunogenicity following a significant change to the manufacturing process from the list of safety concerns.

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 the clinical trial exposure data with a DLP of 26 September 2020	Version 36.0; 11 December 2020
SIV: Populations Not Studied in Clinical Trials		
SIV.2: Limitations to Detect Adverse Reactions in Clinical Trial Development Programs	Updated limitations common to all clinical trials	Version 36.0; 11 December 2020
SIV.3: Limitations in Respect to Populations Typically Under represented in Clinical Trial Development Programs	Updated the special population exposure data, where applicable	Version 36.0; 11 December 2020
SV: Postauthorization Experience	Updated the postmarketing exposure data with a data lock point (DLP) of 26 September 2020	Version 36.0; 11 December 2020
SVII: Details of Important Identified Risks, Important Potential Risks, and Missing Information	Removed the following Important potential risks: • Infection • Osteonecrosis Outside the Jaw Including External Auditory Canal Removed the following Missing information: • Immunogenicity following a significant change to the manufacturing process	Version 36.0; 11 December 2020
SVIII: Summary of the Safety Concerns	Removed the following Important potential risks from the list of safety concerns • Infection • Osteonecrosis Outside the Jaw Including External Auditory Canal Removed the following Missing information: • Immunogenicity following a significant change to the manufacturing process	Version 36.0; 11 December 2020

Part/Module/Annex	Major Change(s)	Version Number and Date
Part V: Risk Minimization Measures (Including Evaluation of The Effectiveness of Risk Minimization Activities)	Aligned with the changes in Module SVII	Version 36.0; 11 December 2020
Part VI: Summary of The Risk Management Plan	Aligned with the changes in Module SVII	Version 36.0; 11 December 2020

Other RMP versions under evaluation:	
RMP version number:	None
Submitted on:	Not applicable
Procedure number:	Not applicable
Details of the currently approved RMP:	
Version number:	35.0
Approved with procedure:	EMEA/H/C/002173/II/0072/G
Date of approval (opinion date):	11 June 2020
Qualified Person for Pharmacovigilance (QPPV) Name:	Raphaël Van Eemeren, MSc Pharm and MSc Ind, Pharm
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorization holder´s QPPV. The electronic signature is available on file.

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List of Abbreviations

Term/Abbreviation	Explanation
ADR	adverse drug reaction
AFF	atypical femoral fracture
AIDS	acquired immune deficiency syndrome
AAOMS	American Association of Oral Maxillofacial Surgeons
ATC	Anatomical Therapeutic Chemical
AAC	area above the curve
BCAT	breast cancer adjuvant therapy
CKD	chronic kidney disease
COX-2	cyclooxygenase-2
CrCl	creatinine clearance
CRPC	castrate-resistant prostate cancer
CV	cardiovascular
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ER	emergency room
EU	European Union
GCTB	giant cell tumor of bone
HALT	hormone ablation therapy
HCM	hypercalcemia of malignancy
HIV	human immunodeficiency virus
IgG	immunoglobulin G
INN	International Nonproprietary Name
iPTH	intact parathyroid hormone
IV	intravenous or intravenously
MAH	marketing authorization holder
MM	multiple myeloma
NPM	new primary malignancy
NSCLC	stage IV untreated non-small cell lung carcinoma with or without bone metastasis
ONJ	osteonecrosis of the jaw
OPG	osteoprotegerin

[redacted]

AMGEN®

Term/Abbreviation	Explanation
PI	Product Information
PIL	Patient Information Leaflet
PMGCTB	primary malignant giant cell tumor of bone
PMO	postmenopausal osteoporosis
PSUR	Periodic Safety Update Report
PTH	parathyroid hormone
PY	person-years of follow-up
Q4W	every 4 weeks
QPPV	Qualified Person for Pharmacovigilance
RA	Rheumatoid arthritis
RANK	receptor activator of nuclear factor kappa-B
RANKL	RANK ligand
RMP	risk management plan
SC	subcutaneous
SmPC	Summary of Product Characteristics
SRE	skeletal-related event
ULN	upper limit of normal
US	United States
ZA	zoledronic acid

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 applicant or marketing authorization holder (MAH)	Amgen Europe B.V.
Medicinal products to which this Risk Management Plan (RMP) refers	1
Invented name(s) in the European Economic Area (EEA)	XGEVA®
Marketing authorization procedure	Centralized
Brief description of the product	
Chemical class	Denosumab is a fully human immunoglobulin G2 (IgG) monoclonal antibody.
Summary of mode of action	Denosumab has high affinity and specificity for the soluble and cell membrane-bound forms of human receptor activator of nuclear factor kappa-B (RANK) ligand (RANKL).
Important information about its composition	Denosumab is derived from the Xeno-mouse™ technology and produced in in genetically engineered mammalian (Chinese hamster ovary) cells.
Hyperlink to the Product Information (PI)	Link to XGEVA PI on EMA website: https://www.ema.europa.eu/en/medicines/human/EPAR/xgeva
Indication(s) in the EEA	
Current	Prevention of skeletal-related events (SREs) (pathological fracture, radiation to bone, spinal cord compression, or surgery to bone) in adults with advanced malignancies involving bone. Treatment of adults and skeletally mature adolescents with giant cell tumor of bone (GCTB) that is unresectable or where surgical resection is likely to result in severe morbidity.
Proposed	Not applicable.

Table 1. Product Overview

Dosage in the EEA	
Current	The recommended dose of XGEVA for prevention of SREs is 120 mg administered as a single subcutaneous (SC) injection once every 4 weeks (Q4W) into the thigh, abdomen, or upper arm. Patients must be adequately supplemented with calcium and vitamin D. The recommended dose of XGEVA for treatment of adults or skeletally mature adolescents with GCTB is 120 mg Q4W administered as an SC injection, with additional 120 mg SC injections on days 8 and 15 of treatment of the first month of therapy.
Proposed	Not applicable.
Pharmaceutical form(s) and strength(s)	
Current	Denosumab is supplied in vials as a sterile, preservative-free solution intended for SC injection. The vial presentation contains 120 mg of denosumab at 70 mg/mL.
Proposed	Not applicable
Is/will the product be subject to additional monitoring in the European Union (EU)?	Yes

PART II. SAFETY SPECIFICATION

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

Table 2. Summary of Epidemiology of Bone Metastases From Solid Tumors

Incidence	Bone metastases are most commonly associated with cancers of the prostate, lung, and breast, with incidence rates as high as 75% of patients with metastatic disease (Selvaggi and Scagliotti, 2005; Carlin and Andriole, 2000; Coleman, 1997; Viadana et al, 1973).
Prevalence	Bone metastases occur in more than 1.5 million patients with cancer worldwide (Coleman and Brown, 2005). At autopsy nearly 70% of patients with breast or prostate cancer and roughly 40% of those dying with lung cancer have evidence of metastatic bone disease (Buijs and Pluijm, 2009).
Demographics of population in the authorized indication and risk factors for the disease	Bone metastases from solid tumors occur in both men and women; the incidence increases with age and higher stage at initial tumor diagnosis (Jensen et al, 2011; Norgaard et al, 2010).
Main existing treatment options	In addition to systemic antitumor therapy, intravenous (IV) bisphosphonates (eg, zoledronic acid [Zometa®, 2011; Zometa®, 2010]) are approved for patients with bone metastases to reduce the risk of developing SREs (Carlson et al, 2008; Theriault et al, 2006; Warr and Johnston, 2004; Hillner et al, 2003).
Natural history of the indicated condition in the population, including mortality and morbidity	Bone metastases are associated with significant skeletal morbidity (ie, SREs, including fractures, radiation to bone, spinal cord compression, and surgery to bone) (Coleman, 2006; Roodman, 2004; Yonou et al, 2004). Worldwide, approximately 1 million of 1.8 million people who die with breast, prostate, or lung cancer annually have bone metastases (Parkin et al, 2005).
Important comorbidities	• cardiovascular (CV) disease (Li et al, 2012; Nguyen et al, 2011; Lloyd-Jones et al, 1999) • malignancy (Dimopoulos et al, 2012; Liu et al, 2011; Curtis et al, 2006; Mellemkjaer et al, 2006; Smith et al, 2003; Thellenberg et al, 2003; Evans et al, 2001; Tanaka et al, 2001; Bergman et al, 2000; Chaplain et al, 2000; Volk and Pompe-Kirn, 1997; Diamandidou et al, 1996) • infection (Li et al, 2012) For comedications, XGEVA is required to be administered in conjunction with adequate supplementation of calcium and vitamin D unless hypercalcemia is present. XGEVA is administered in conjunction with standard antineoplastic and/or supportive therapies as appropriate for the indicated populations.

Table 3. Summary of Epidemiology of Giant Cell Tumor of Bone (GCTB)

Incidence	Giant cell tumor of bone occurs in approximately 1 person per million per year (Liede et al, 2014). Each year, approximately 800, 800, 80, and 30 cases of GCTB are newly diagnosed in the United States (US), EU, Canada, and Australia, respectively.
Prevalence	Giant cell tumor of bone accounts for 5% of all primary bone tumors and 20% of benign skeletal tumors in the Western world (Liede et al, 2014; Chakarun et al, 2013; Kim et al, 2012). As of 31 December 2013, an estimated 1581 to 2153 individuals had a diagnosis of benign GCTB within the previous 5 years (Liede et al, 2014). Similarly, the 3-year prevalence estimates in 2013 were 951 and 1295 individuals in the US (Liede et al, 2014).
Demographics of population in the authorized indication and risk factors for the disease	Giant cell tumor of bone typically occurs in young adults. The median age at diagnosis (Swedish Cancer Registry data) is estimated at 34 years (interquartile range 25, 50 years), and the highest incidence per million is among individuals 20 to 39 years old (Amelio et al, 2016). Population-based data in Sweden and Japan estimate 39% to 55% of patients are diagnosed between age 20 and 39 years (Rockberg et al, 2015). Women comprise half or more of the affected population (Amelio et al, 2016; Rockberg et al, 2015).
Main existing treatment options	Surgery can be curative if adequate resection of the tumor is performed (Civista Health, 2012; Malawer et al, 2011; Singer et al, 2011). For patients with unresectable GCTB, denosumab is presently the only approved therapy.
Natural history of the indicated condition in the population, including mortality and morbidity	When left untreated, GCTB may progress to complete destruction of the affected bone and massive tumor formation. Leggon et al (2004) reported that 21% of patients with GCTB of the pelvis or spine died during an average follow-up of 8.7 years (Leggon et al, 2004). Local recurrence rates vary from 10% to 40% post-surgery; most recurrences occur within 24 months of surgery (Klenke et al, 2011; Arbeitsgemeinschaft et al, 2008; Malek et al, 2006; Prosser et al, 2005; Blackley et al, 1999; Lausten et al, 1996; Campanacci et al, 1987; Goldenberg et al, 1970; Hutter et al, 1962).
Important comorbidities	For comedications, XGEVA is required to be administered in conjunction with adequate supplementation of calcium and vitamin D unless hypercalcemia is present. XGEVA is administered in conjunction with standard antineoplastic and/or supportive therapies as appropriate for the indicated populations.

Table 4. Summary of Epidemiology of Multiple Myeloma

Incidence	The worldwide age standardized incidence of multiple myeloma is 1.5 cases per 100 000 persons per year overall (114 251 cases); 1.7 among men and 1.2 among women (GLOBOCAN, 2012). Incidence per 100 000 per year ranges from 0.9 in Africa to 2.5 in Europe and 2.6 in the Americas.
Prevalence	The 5-year prevalence is 4.4 per 100 000 adults (229 468 cases). The 5-year prevalence proportion per 100 000 ranges from 1.3 in Africa to 12.6 in Europe and 9.4 in the Americas.
Demographics of population in the authorized indication and risk factors for the disease	The median age at diagnosis is approximately 70 years (Siegel et al, 2015). Multiple myeloma is more common in men than in women. Black race, older age, and high body mass index are risk factors (American Cancer Society, accessed 3 Nov 2016; Myeloma Risk Factors, accessed 3 Nov 2016; Wallin and Larsson, 2011; Landgren and Weiss, 2009). Risk is 2.3 times higher in people with an affected first-degree relative compared with the general population (American Cancer Society, accessed 3 Nov 2016; Frank et al, 2014). Multiple myeloma risk is higher among individuals with systemic lupus erythematosus (Apor et al, 2014), autoimmune hemolytic anemia (Shen et al, 2014), ankylosing spondylitis or pernicious anemia (McShane et al, 2014), and lower in those with psoriasis (Shen et al, 2014).
Main existing treatment options	Currently, IV bisphosphonates (eg, zoledronic acid [Zometa®, 2010; Zometa®, 2011] and pamidronate [Aredia®, 2009]) are the standard of care for the prevention of SREs in patients with multiple myeloma (Bird et al, 2011). The benefits of bisphosphonate treatment have been seen in patients with symptomatic multiple myeloma, even in the absence of evident bone lesions. However, bisphosphonates are known for adverse effects on renal function. Renal impairment is a common condition in patients with multiple myeloma which may increase risk of early death. (Augustson et al, 2005; Knudsen et al, 1994).
Natural history of the indicated condition in the population, including mortality and morbidity	• Multiple myeloma is an incurable hematological neoplastic disorder characterized by uncontrolled proliferation of malignant plasma cells in the bone marrow (Multiple Myeloma Research Foundation, 2012; Durie, 2011; Palumbo and Anderson, 2011). Clinically, multiple myeloma is characterized by hypercalcemia, renal impairment (Qian et al, 2015), anemia, consequences of light chain deposition (amyloid), reduction in normal gamma globulins (immune paresis), and increased risk of infection. At diagnosis, up to 8% to 15% of patients are asymptomatic (Kyle and Rajkumar, 2004), up to 96% have bone marrow involvement (Kyle et al, 2003), and 70 to 80% have bone lesions.

Table 4. Summary of Epidemiology of Multiple Myeloma

Natural history of the indicated condition in the population, including mortality and morbidity (continued)	Typically, the severity of bone destruction correlates with disease burden (including SRE) and prognosis (Terpos et al, 2003). Osteoclast activity may also contribute to myeloma cell survival, growth, and resistance to apoptosis (Yaccoby et al, 2004). Thus, controlling further progression of myeloma bone disease may have direct consequences on both survival and quality of life for myeloma patients. Approximately 61% of multiple myeloma patients experience renal impairment, with 50% having chronic kidney disease (CKD) (median follow-up: 434 days) (Qian et al, 2015). Almost 47% of diagnosed patients survive 5-years or longer (Siegel et al, 2015). High-dose chemotherapy with autologous stem cell support and targeted treatments (eg, thalidomide, bortezomib, and lenalidomide) have improved survival (Costa et al, 2016; Mateos and San Miguel, 2013), with younger patients benefiting the most (Pulte et al, 2015; Kumar et al, 2014; Schaapveld et al, 2010; Kristinsson et al, 2007). The age-standardized mortality rate is 1.0 per 100 000 persons per year (GLOBOCAN, 2012), and ranges from 0.6 in Southeast Asia to 1.4 in Europe and 1.6 in the Americas.
Important comorbidities	• cardiovascular disease (Li et al, 2012; Nguyen et al, 2011; Lloyd-Jones et al, 1999) • malignancy (Dimopoulos et al, 2012; Liu et al, 2011; Curtis et al, 2006; Mellemkjaer et al, 2006; Smith et al, 2003; Thellenberg et al, 2003; Evans et al, 2001; Tanaka et al, 2001; Bergman et al, 2000; Chaplain et al, 2000; Volk and Pompe-Kirn, 1997; Diamandidou et al, 1996) • infection (Li et al, 2012) • renal impairment (Gavriatopoulou et al, 2016; Qian et al, 2015; Dimopoulos et al, 2014; Blade et al, 2005) For comedications, XGEVA is required to be administered in conjunction with adequate supplementation of calcium and vitamin D unless hypercalcemia is present. XGEVA is administered in conjunction with standard antineoplastic and/or supportive therapies as appropriate for the indicated populations.

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

Table 5. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings (High Level Summary)	Relevance to Human Usage
Toxicity • Reproductive toxicity	Denosumab had no effect on female fertility or male reproductive organs in monkeys at exposures that were 9.5- to 16-fold higher, respectively, than the human exposure at 120 mg SC administered once Q4W. In a study of cynomolgus monkeys dosed with denosumab during the period equivalent to the first trimester at area above the curve (AAC) exposures up to 10-fold higher than the human dose (120 mg Q4W), there was no evidence of maternal or fetal harm. In this study, fetal lymph nodes were not examined. In another study of cynomolgus monkeys dosed with denosumab throughout pregnancy at AAC exposures 12-fold higher than the human dose (120 mg every 4-weeks), there were increased stillbirths and postnatal mortality; abnormal bone growth resulting in reduced bone strength, reduced hematopoiesis, and tooth malalignment; absence of peripheral lymph nodes; and decreased neonatal growth. There was no evidence of maternal harm prior to labor; adverse maternal effects occurred infrequently during labor. Maternal mammary gland development was normal.	XGEVA 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 XGEVA. It is not known if denosumab is excreted in human milk. Because denosumab has the potential to cause adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug. Use in pregnant and lactating women is not considered a safety concern in this RMP.

Table 5. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings (High Level Summary)	Relevance to Human Usage
Toxicity (continued) • Developmental toxicity	Denosumab has been shown to be a potent inhibitor of bone resorption by inhibition of RANKL. Adolescent primates dosed with denosumab at 2.8 and 15 times (10 and 50 mg/kg dose) the clinical exposure based on AAC had abnormal growth plates. 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 largely returned to normal; there were no adverse effects on tooth eruption; and minimal to moderate mineralization in multiple tissues was seen in one recovery animal. In neonatal rats, inhibition of RANKL (target of denosumab therapy) was associated with inhibition of bone growth, altered growth plates, and inhibited tooth eruption, and these changes were partially reversible upon cessation of RANKL inhibition.	The safety and efficacy of XGEVA have not been established in pediatric patients other than skeletally mature pediatric patients with GCTB. Treatment with denosumab may impair bone growth in children with open growth plates and may inhibit eruption of dentition. XGEVA 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 XGEVA.
Safety pharmacology	Not applicable	Not applicable
Other toxicity-related information or data	Not applicable	Not applicable

Part II: Module SIII - Clinical Trial Exposure

Table 6. Total Subject Exposure to Denosumab in Clinical Trials by Product, Indication, and Duration
Safety Analysis Set

	Exposure to Denosumab by Duration										
PRODUCT Indication	≥ 1 Year n (subj-yrs)	≥ 2 Years n (subj-yrs)	≥ 3 Years n (subj-yrs)	≥ 4 Years n (subj-yrs)	≥ 5 Years n (subj-yrs)	≥ 6 Years n (subj-yrs)	≥ 7 Years n (subj-yrs)	≥ 8 Years n (subj-yrs)	≥ 9 Years n (subj-yrs)	≥ 10 Years 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 (450.0)
XGEVA											
CRPC	574 (1612.3)	342 (1265.4)	198 (899.8)	94 (551.0)	66 (427.5)	39 (276.5)	13 (107.5)	5 (47.8)	4 (38.9)	1 (10.1)	840 (1771.8)
BCAT[a]	1986 (8263.1)	1772 (7948.4)	1594 (7507.5)	1441 (6974.3)	183 (933.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2241 (8392.0)
GCTB	459 (1880.0)	319 (1683.3)	248 (1507.7)	190 (1307.2)	144 (1099.5)	104 (879.4)	76 (699.6)	55 (541.5)	36 (379.5)	26 (285.1)	548 (1935.9)
HCM	2 (3.5)	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)	33 (10.0)
MM	19 (46.0)	10 (33.7)	6 (24.0)	3 (14.0)	1 (5.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	95 (72.3)
SRE Solid Tumor[b]	1705 (3866.7)	766 (2453.7)	338 (1424.8)	155 (776.3)	52 (317.5)	18 (133.7)	7 (63.0)	4 (40.4)	4 (40.4)	2 (21.6)	3598 (4758.5)
SRE MM	941 (2545.4)	557 (1901.7)	321 (1346.5)	163 (799.8)	76 (414.9)	6 (37.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1268 (2706.1)
NSCLC	37 (54.6)	5 (10.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	145 (101.9)
Total	5723 (18271.6)	3771 (15297.1)	2705 (12710.3)	2046 (10422.6)	522 (3198.0)	167 (1326.8)	96 (870.2)	64 (629.8)	44 (458.9)	29 (316.8)	8768 (19748.4)

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

Table 6. Total Subject Exposure to Denosumab in Clinical Trials by Product, Indication, and Duration
Safety Analysis Set

	Exposure to Denosumab by Duration										
PRODUCT Indication	≥ 1 Year n (subj-yrs)	≥ 2 Years n (subj-yrs)	≥ 3 Years n (subj-yrs)	≥ 4 Years n (subj-yrs)	≥ 5 Years n (subj-yrs)	≥ 6 Years n (subj-yrs)	≥ 7 Years n (subj-yrs)	≥ 8 Years n (subj-yrs)	≥ 9 Years n (subj-yrs)	≥ 10 Years n (subj-yrs)	Total n (subj-yrs)
Prolia total	11 174 (49 378.8)	8193 (45 075.1)	6127 (39 752.2)	4857 (35 525.7)	4076 (31 928.9)	3485 (28 728.2)	2381 (21 231.6)	1633 (15 877.0)	1388 (13 826.2)	515 (5173.0)	13972 (51 788.8)
Total all studies	16 897 (67 650.4)	11 964 (60 372.1)	8832 (52 462.5)	6903 (45 948.3)	4598 (35 126.9)	3652 (30 055.0)	2477 (22 101.8)	1697 (16 506.8)	1432 (14 285.0)	544 (5489.8)	24179 (71 987.2)

BCAT = Breast cancer adjuvant therapy; CRPC = castrate-resistant prostate cancer; GCTB = giant cell tumor of bone; HCM = hypercalcemia of malignancy; MM = multiple myeloma; NSCLC = stage IV untreated non-small cell lung carcinoma with or without bone metastasis; SRE = skeletal related events

n = number of subjects exposed to denosumab; subj-yrs = total subject-years of exposure.

[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.

Data from ongoing and completed studies as of 26 September 2020. Ongoing Prolia studies included 20130173, 20140444, 20050209, and 20170534. Ongoing XGEVA studies include 20140114 and 20180142. 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 as (the last non-missing dose date - first non-missing dose date + 1 day + 180 days)/365.25.

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 as (the last non-missing dose date - first non-missing dose date + 1 day + 28 days)/365.25.

For previous risk management plan, subject-years of follow-up instead of subject-years of exposure at the subject level was measured from the first dose date to the earlier of end of study date or snapshot date.

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Table 7. Total Subject Exposure to Denosumab 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 (147.5)	32 (12.3)	16 (5.5)	5 (1.5)
XGEVA							
CRPC	0 (0.0)	0 (0.0)	0 (0.0)	141 (333.3)	317 (674.3)	307 (623.3)	75 (140.8)
BCAT[a]	NA	NA	NA	NA	NA	NA	NA
GCTB	0 (0.0)	0 (0.0)	5 (17.0)	223 (768.6)	8 (20.5)	2 (6.9)	0 (0.0)
HCM	0 (0.0)	0 (0.0)	0 (0.0)	13 (4.3)	7 (0.9)	1 (0.2)	0 (0.0)
MM	0 (0.0)	0 (0.0)	0 (0.0)	30 (15.2)	21 (12.7)	6 (2.5)	0 (0.0)
SRE Solid Tumor[b]	0 (0.0)	0 (0.0)	0 (0.0)	679 (701.7)	586 (721.0)	393 (444.5)	43 (51.9)
SRE MM	0 (0.0)	0 (0.0)	0 (0.0)	382 (853.9)	198 (420.8)	90 (146.9)	10 (11.5)
NSCLC	0 (0.0)	0 (0.0)	0 (0.0)	43 (30.6)	34 (23.2)	17 (9.9)	0 (0.0)
Total	0 (0.0)	0 (0.0)	5 (17.0)	1511 (2707.7)	1171 (1873.5)	816 (1234.1)	128 (204.2)
Prolia total	17 (33.7)	27 (68.7)	45 (109.6)	337 (560.5)	688 (1428.9)	607 (1372.3)	68 (168.5)
Total male	17 (33.7)	27 (68.7)	50 (126.6)	2369 (3415.7)	1891 (3314.6)	1439 (2611.9)	201 (374.1)

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

Table 7. Total Subject Exposure to Denosumab 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							
Phase 1 studies	0 (0.0)	0 (0.0)	0 (0.0)	780 (248.7)	68 (28.6)	13 (4.7)	4 (1.3)
XGEVA							
CRPC	NA	NA	NA	NA	NA	NA	NA
BCAT[a]	0 (0.0)	0 (0.0)	0 (0.0)	1949 (7306.7)	258 (970.0)	33 (110.3)	1 (4.9)
GCTB	0 (0.0)	0 (0.0)	23 (70.2)	274 (1023.4)	10 (22.4)	3 (6.9)	0 (0.0)
HCM	0 (0.0)	0 (0.0)	0 (0.0)	6 (2.5)	4 (1.5)	1 (0.5)	1 (0.1)
MM	0 (0.0)	0 (0.0)	0 (0.0)	24 (23.3)	10 (10.5)	3 (4.9)	1 (3.2)
SRE Solid Tumor[b]	0 (0.0)	0 (0.0)	0 (0.0)	1376 (2109.2)	398 (579.3)	108 (133.8)	15 (17.0)
SRE MM	0 (0.0)	0 (0.0)	0 (0.0)	334 (782.3)	164 (344.3)	78 (123.8)	12 (22.7)
NSCLC	0 (0.0)	0 (0.0)	0 (0.0)	31 (22.4)	16 (13.9)	3 (1.2)	1 (0.9)
Total	0 (0.0)	0 (0.0)	23 (70.2)	3994 (11269.8)	860 (1941.8)	229 (381.6)	31 (48.7)
Prolia total	22 (42.4)	26 (59.8)	30 (67.4)	3357 (9280.7)	6124 (28020.4)	2505 (10274.1)	119 (301.7)
Total female	22 (42.4)	26 (59.8)	53 (137.6)	8131 (20799.2)	7052 (29990.8)	2747 (10660.4)	154 (351.6)

BCAT = Breast cancer adjuvant therapy; CRPC = castrate-resistant prostate cancer; GCTB = giant cell tumor of bone; HCM = hypercalcemia of malignancy; MM = multiple myeloma; NSCLC = stage IV untreated non-small cell lung carcinoma with or without bone metastasis; SRE = skeletal related events

n = number of subjects exposed to denosumab; subj-yrs = total subject-years of exposure.

[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.

Data from ongoing and completed studies as of 26 September 2020. Ongoing Prolia studies included 20130173, 20140444, 20050209, and 20170534. Ongoing XGEVA studies include 20140114 and 20180142. 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 earlier of date of last non-missing dose – 1 day + 180 days and end of study date.
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 earlier of ([date of last non-missing dose – 1 day + 28 days], and end of study date).
For previous risk management plan, subject-years of follow-up instead of subject-years of exposure at the subject level was measured from the first dose date to the earlier of end of study date or snapshot date.
Program: /userdata/stat/amg162/meta/pool_studies/analysis/rmp2020/tables/t-exposure-xgeva-age-sex.sas.
Output: t14-05-001-006-exposure-xgeva-age-sex.rtf (Date Generated: 02DEC2020:05:48) Source Data: d202009.dsur_exp.

Table 8. 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-yr)	120 mg n (subj-yr)	> 120 mg n (subj-yr)
Phase 1	65 (0.1)	554 (0.1)	24 (0.1)	65 (5.2)	554 (45.7)	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 (3.5)	0 (0.0)	0 (0.0)	548 (1935.9)	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 (19674.4)	187 (86.8)

BCAT = Breast cancer adjuvant therapy; CRPC = castrate-resistant prostate cancer; GCTB = giant cell tumor of bone; HCM = hypercalcemia of malignancy; MM = multiple myeloma; NSCLC = stage IV untreated non-small cell lung carcinoma with or without bone metastasis; SRE = skeletal related events

n = number of subjects exposed to denosumab; subj-yrs = total subject-years of exposure.

[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.

Data from ongoing and completed XGEVA studies as of 26 September 2020. Ongoing XGEVA studies include 20140114 and 20180142.

Safety Analysis Set includes subjects who received at least 1 dose of investigational product.

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 earlier of ([date of last non-missing dose – 1 day + 28 days], and end of study date).

For previous risk management plan, subject-years of follow-up instead of subject-years of exposure at the subject level was measured from the first dose date to the earlier of end of study date or snapshot date.

Program: /userdata/stat/amg162/meta/pool_studies/analysis/rmp2020/tables/t-exposure-xgeva-dose.sas

Output: t14-05-001-008-exposure-xgeva-dose.rtf (Date Generated: 02DEC2020:22:46) Source Data: adam.aslinfo.

Table 9. Total Subject Exposure to Denosumab in Clinical Trials by Product and Race/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 (374.9)	186 (32.2)	33 (16.4)	67 (20.0)	24 (6.5)	0 (0.0)	1439 (450.0)
XGEVA							
CRPC	707 (1465.6)	47 (98.6)	36 (85.6)	22 (33.1)	26 (83.7)	2 (5.2)	840 (1771.8)
BCAT[a]	1664 (6309.5)	74 (265.4)	135 (444.1)	345 (1307.1)	23 (65.7)	0 (0.0)	2241 (8392.0)
GCTB	448 (1539.9)	32 (118.4)	30 (152.0)	28 (86.0)	10 (39.4)	0 (0.0)	548 (1935.9)
HCM	23 (7.5)	7 (2.0)	1 (0.2)	1 (0.1)	1 (0.1)	0 (0.0)	33 (10.0)
MM	73 (59.8)	11 (6.8)	4 (0.8)	5 (1.9)	2 (3.0)	0 (0.0)	95 (72.3)
SRE Solid Tumor[b]	2989 (3977.4)	95 (112.2)	266 (281.6)	193 (307.8)	55 (79.5)	0 (0.0)	3598 (4758.5)
SRE MM	1048 (2282.5)	44 (82.2)	0 (0.0)	159 (312.3)	17 (29.1)	0 (0.0)	1268 (2706.1)
NSCLC	130 (92.6)	7 (4.5)	0 (0.0)	5 (3.6)	3 (1.3)	0 (0.0)	145 (101.9)
Total	7082 (15734.9)	317 (690.2)	472 (964.4)	758 (2051.9)	137 (301.8)	2 (5.2)	8768 (19748.4)

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

Table 9. Total Subject Exposure to Denosumab in Clinical Trials by Product and Race/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)
Prolia total	12737 (47978.5)	146 (476.7)	708 (2742.7)	288 (425.5)	93 (165.4)	0 (0.0)	13972 (51788.8)
Total all studies	20948 (64088.3)	649 (1199.1)	1213 (3723.5)	1113 (2497.4)	254 (473.7)	2 (5.2)	24179 (71987.2)

BCAT = Breast cancer adjuvant therapy; CRPC = castrate-resistant prostate cancer; GCTB = giant cell tumor of bone; HCM = hypercalcemia of malignancy; MM = multiple myeloma; NSCLC = stage IV untreated non-small cell lung carcinoma with or without bone metastasis; SRE = skeletal related events

n = number of subjects exposed to denosumab; subj-yrs = total subject-years of exposure.

[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.

Data from ongoing and completed studies as of 26 September 2020. Ongoing Prolia studies included 20130173, 20140444, 20050209, and 20170534. Ongoing XGEVA studies include 20140114 and 20180142. 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 earlier of ([date of last non-missing dose – 1 day + 180 days], and end of study date).

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 earlier of ([date of last non-missing dose – 1 day + 28 days], and end of study date).

For previous risk management plan, subject-years of follow-up instead of subject-years of exposure at the subject level was measured from the first dose date to the earlier of end-of-study date or snapshot date.

Program: /userdata/stat/amg162/meta/pool_studies/analysis/rmp2020/tables/t-exposure-xgeva-race-ethnic.sas.

Output: t14-05-001-007-exposure-xgeva-race-ethnic.rtf (Date Generated: 02DEC2020:05:49) Source Data: d202009.dsur_exp.

Table 10. Total Subject Exposure to Denosumab 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 (98.6)
Moderate	42 (18.7)
Severe	26 (6.7)
Kidney failure	22 (6.1)
Total	360 (130.2)
PROLIA	
Mild	6815 (26469.1)
Moderate	3943 (15851.3)
Severe	84 (273.8)
Kidney failure	2 (6.7)
Total	10844 (42601.0)
XGEVA	
Mild	2293 (4406.6)
Moderate	1154 (1853.8)
Severe	36 (50.2)
Kidney failure	2 (1.8)
Total	3485 (6312.4)
Overall total	
Mild	9378 (30373.3)
Moderate	5139 (17549.3)
Severe	146 (330.7)
Kidney failure	26 (14.6)
Total	14689 (48267.9)

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

[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).

Data from ongoing and completed studies as of 26 September 2020. Ongoing Prolia studies included 20130173, 20140444, 20050209, and 20170534. Ongoing XGEVA studies include 20140114 and 20180142. 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 earlier of ([date of last non-missing dose - 1 day + 180 days], and end of study date).

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 earlier of ([date of last non-missing dose - 1 day + 28 days], and end of study date).

For previous risk management plan, subject-years of follow-up instead of subject-years of exposure at the subject level was measured from the first dose date to the earlier of end-of-study date or snapshot date.
Program: /userdata/stat/amg162/meta/pool_studies/analysis/rmp2020/tables/t-exposure-renal.sas.
Output: t14-05-001-009-exposure-renal.rtf (Date Generated: 02DEC2020:22:47) 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 11. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Severe, untreated hypocalcemia	Pre-existing hypocalcemia must be corrected prior to initiating therapy with XGEVA.	No	It is a contraindication in the Summary of Product Characteristics (SmPC).
Hypersensitivity to the active substance or to any of the excipients	Patients who are hypersensitive to denosumab or to any of the excipients should not receive XGEVA.	No	It is a contraindication in the SmPC.
Unhealed lesions from dental or oral surgery	While on treatment, invasive dental procedures should be performed only after careful consideration and be avoided in close proximity to XGEVA administration.	No	It is a contraindication in the SmPC.
Patients with prior intravenous bisphosphonate treatment	For randomized, controlled trials, prior IV bisphosphonate treatment confounds the determination of efficacy. For all trials, it may increase the risk for safety events such as osteonecrosis of the jaw (ONJ).	Yes	Not applicable.
Current or prior bisphosphonate treatment	Use of bisphosphonates would interfere with the ability to assess denosumab's efficacy in clinical studies.	No	Data are available for 795 subjects in advanced cancer settings and an additional 19 subjects that received XGEVA from the multiple myeloma pivotal study who had previously received bisphosphonates.

Table 11. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Current or prior bisphosphonate treatment (continued)			Amgen also conducted a study of denosumab in cynomolgus monkeys transitioned from bisphosphonate therapy and 2 clinical studies of bisphosphonate-transition in bone loss settings. Results from these studies did not demonstrate an increased risk of skeletal adverse effects over the period exposed in patients who received denosumab following bisphosphonate use. Therefore, no special dosing recommendations or limitation of use for patients previously treated with bisphosphonates are considered necessary in the SmPC.
Exclusion Criteria for SRE (Multiple myeloma and Solid Tumor) only			
Patients with severe renal impairment Calculated creatinine clearance (CrCl) < 30 mL/min	Prescribing information for zoledronic acid states that use is not recommended in patients with severe renal impairment (defined as a CrCl < 30 mL/min calculated using the Cockcroft-Gault equation). Because zoledronic acid was the comparator agent used in the 4 pivotal denosumab SRE Solid Tumor studies, subjects with a CrCl < 30 mL/min were excluded from study participation.	No	Clinical study data for subjects with severe renal impairment (CrCl < 30 mL/min) including subjects receiving dialysis (317 subjects at time of initial registration and a post registration pharmacology study of patients with CKD, Study 20101361) have demonstrated an increased risk for hypocalcemia including severe hypocalcemia. Changes in serum phosphorus and magnesium were small and there were few adverse events of hypophosphatemia or hypomagnesemia. Small increases in intact parathyroid hormone (iPTH) over time were seen in the CKD on dialysis group.

Table 11. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Exclusion Criteria for GCTB only			
Skeletally immature children and adolescents	Because treatment of juvenile rats and neonatal and adolescent cynomolgus monkeys resulted in widening of epiphyseal plates and because GCTB is rare in skeletally immature children and adolescents, skeletally immature subjects were excluded.	No	Denosumab is not indicated for treatment in children or skeletally immature adolescents.
Current receipt of other GCTB-specific treatment	Use of any other GCTB-specific treatment would interfere with the ability to assess denosumab's efficacy.	No	Because other treatments may interfere with the ability to assess denosumab efficacy, but it does not represent contraindication for the use of denosumab concomitantly with other putative treatments for GCTB (with the exception of bisphosphonates as indicated in the warnings and precautions section of the SmPC).
Known or suspected current diagnosis of underlying bone malignancy or brown tumor of bone	The presence of osteosarcoma or brown tumor of bone could interfere with the ability to assess denosumab's efficacy on GCTB.	No	Narrow indication (denosumab is not indicated for primary bone malignancy or brown tumor of bone).

Table 11. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Exclusion Criteria for SRE (Multiple Myeloma only)			
Nonsecretory multiple myeloma based upon standard M-component criteria (ie, measurable serum/urine M-component) unless the baseline serum free-light chain level is elevated	Assessments of disease progression were based on International Myeloma Working Group criteria, which may include M protein or free-light chains. It is difficult to track disease progression based on standard assays for M protein or free-light chains in this population.	No	It is a diagnostic criterion, not a safety-related disease-specific criterion or contraindication.

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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 XGEVA and the mechanism of action, the XGEVA clinical development program is able to detect rare and very rare adverse drug reactions (ADRs), as well as ADRs associated with prolonged exposure or long latency (Table 12).

Table 12. Limitations Common to All Clinical Trials

Ability to Detect Adverse Drug Reactions (ADRs)	Limitation of Trial Program	Discussion of Implications for Target Population
Very rare and rare ADRs	3598 subjects were exposed to XGEVA in the clinical study program for the SRE Solid Tumor indication. 548 Subjects were exposed to XGEVA for the GCTB indication. 1268 subjects were exposed to XGEVA for the SRE multiple myeloma indication. In total, 9075 subjects have received 1 or more doses of denosumab 120 mg.	For very rare ADRs (frequency < 0.01%), the chance of observing at least 1 case was less than 30% in the clinical study program for the SRE Solid Tumor indication and less than 12% for the SRE multiple myeloma indication. In the clinical study program, the chance of observing at least 1 rare ADR (frequency ≥ 0.01% and < 0.1%) was ≥ 30% to < 97% for the SRE Solid Tumor indication and ≥ 12% to < 72% for the SRE multiple myeloma indication. There was a ≥ 80% chance of observing at least 1 case of ADRs with a frequency ≥ 0.045% in SRE Solid Tumor studies and a frequency of ≥ 0.127% for SRE multiple myeloma studies. Overall, the chance of observing at least 1 case of very rare or rare ADR with denosumab 120 mg is < 60% and ≥ 60%, respectively.

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Table 12. Limitations Common to All Clinical Trials

Ability to Detect Adverse Drug Reactions (ADRs)	Limitation of Trial Program	Discussion of Implications for Target Population
ADRs due to prolonged exposure	8768 subjects were exposed to XGEVA in the clinical studies with a total 19748.4 subject-years of denosumab exposure, where 5723 subjects (18271.6 subject-years), 3771 subjects (15297.1 subject years), 2705 subjects (12 710.3 subject years), 2046 subjects (10 422.6 subject years), 522 subjects (3198.0 subject years), and 167 subjects (1326.8 subject years) were exposed for ≥ 1 year, ≥ 2 years, ≥ 3 years, ≥ 4 years, ≥ 5 years, and ≥ 6 years, respectively.	
ADRs with a long latency	8768 subjects were exposed to XGEVA in the clinical studies with a total 19748.4 subject-years of denosumab exposure, where 5723 subjects (18 271.6 subject-years), 3771 subjects (15 297.1 subject-years), 2705 subjects (12 710.3 subject-years), 2046 subjects (10 422.6 subject-years), 522 subjects (3198.0 subject-years), and 167 subjects (1326.8 subject-years) were exposed for ≥ 1 year, ≥ 2 years, ≥ 3 years, ≥ 4 years, ≥ 5 years, and ≥ 6 years, respectively.	The clinical trial program allowed detection of ADRs with a long latency in this high-risk, advanced cancer population.

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

Table 13. (Table SIV.2): Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Fifty-three pregnancies from maternal exposures and pregnant partners of maleswere reported in the XGEVA clinical development program.
Breastfeeding women	No cases of lactation were reported in the XGEVA clinical development program.
Patients with relevant comorbidities	
Patients with hepatic impairment	Patients with hepatic impairment were not specifically excluded from the clinical development program (except for baseline alanine and aspartate aminotransaminases > 5 X upper limit of normal [ULN], total bilirubin > 2 X ULN) and no classification of liver functional status were collected.
Patients with renal impairment	Patients with severe renal impairment were excluded from most registration studies in cancer populations. XGEVA clinical studies included 1154 subjects (1853.8 subject years) with moderate renal impairment and 36 subjects (50.2 subject years) had severe renal impairment or end-stage renal disease at entry.
Patients with cardiovascular impairment	No specific exclusions regarding CV function and no classification of cardiac function status were collected.
Immunocompromised patients	No specific exclusions with exception of human immunodeficiency virus (HIV) positive and no classification of liver functional status were collected.
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the XGEVA clinical development program.
Population with relevant different ethnic origin	Not included in the XGEVA clinical development program.
Subpopulations carrying relevant genetic polymorphisms	No specific exclusions.
Patients ≥ 75 years of age	No eligibility upper limit on age; 1074 subjects (1625.9 subject years) ≥ 75 years and 168 subjects (254.9 subject-years) ≥ 85 years were included in clinical studies.

Part II: Module SV - Postauthorization Experience

SV.1 Postauthorization Exposure

SV.1.1 Method Used to Calculate Exposure

Amgen's estimates of postmarketing patient exposure are in part based on unit sales data (eg, vials or syringes), and in part on observed drug utilization parameters. Worldwide unit sales are recorded monthly by country, and are converted to a monthly estimate of person count (when feasible) or person-time using region and product specific utilization parameters and algorithms. These parameters include the average number of mg per administration, average length of treatment, days between administrations, patient turnover rates, market penetration rates, and average revenue per patient. These drug utilization parameters can change over time to best represent the current patient and market experience.

SV.1.2 Exposure

Table 14. Estimated Number of Patient Years of Exposure to XGEVA, by Region and Demographic Characteristics, in the Postmarketing Setting

Demographic Characteristic	Cumulative Number of Patient-years of Exposure					
	AU	CA	EUR	US	Other[a]	Total
Overall	35 521	25 454	700 762	449 509	122 054	1 333 299
Sex						
Female	29 728	21 303	586 467	376 194	102 147	1 115 838
Male	5793	4152	114 294	73 315	19 907	217 461
Age						
18 - 34	92	66	1822	1169	317	3467
35 - 49	1471	1054	29 012	18 610	5053	55 199
50 - 64	12 329	8835	243 234	156 025	42 365	462 788
65 - 74	8362	5992	164 959	105 814	28 731	313 859
≥ 75	13 267	9507	261 734	167 892	45 587	497 987

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Footnotes defined on last page of table

Table 14. Estimated Number of Patient Years of Exposure to XGEVA, by Region and Demographic Characteristics, in the Postmarketing Setting

Demographic Characteristic	Cumulative Patient-years of Exposure					
	AU	CA	EUR	US	Other[a]	Total
Sex/age						
Female						
18 - 34	78	56	1542	989	269	2933
35 - 49	1336	957	26 349	16 902	4589	50 132
50 - 64	10 823	7756	213 522	136 965	37 190	406 256
65 - 74	6866	4920	135 457	86 890	23 593	257 727
≥ 75	10 624	7613	209 598	134 448	36 506	398 790
Male						
18 - 34	14	10	280	180	49	533
35 - 49	135	97	2663	1708	464	5067
50 - 64	1506	1079	29 712	19 059	5175	56 532
65 - 74	1495	1072	29 502	18 924	5138	56 132
≥ 75	2643	1894	52 137	33 443	9081	99 197

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AU = Australia and New Zealand; CA = Canada; EUR = European Union, European Economic Area, and Switzerland; Other = emerging markets in Asia, Africa, Middle East, and Latin America where Amgen is the marketing authorization holder; US = United States
Note: Numbers may not add to the total due to rounding. Cumulative data to 26 September 2020
Age and sex breakdowns are based on patient characteristics in MarketScan, a US health insurance claims database. Applying these distributions to regions outside the United States requires strong assumptions that are not easily testable.
[a] Does not include Japan. Does not include product distributed in China through BeiGene.

Table 15. Estimated Number of Patients Exposed to XGEVA, by Region and Demographic Characteristics[a], in the Postmarketing Setting

Demographic Characteristic	Cumulative Number of Patients Exposed					
	AU	CA	EUR	US	Other[b]	Total
Overall	46 177	33 090	910 990	584 361	158 670	1 733 288
Sex						
Female	38 645	27 693	762 407	489 051	132 791	1 450 589
Male	7531	5397	148 582	95 309	25 879	282 699
Age						
18 - 34	120	86	2369	1519	413	4507
35 - 49	1912	1370	37 715	24 193	6569	71 758
50 - 64	16 028	11 486	316 204	202 832	55 074	601 624
65 - 74	10 870	7789	214 447	137 559	37 351	408 016
≥ 75	17 247	12 359	340 255	218 259	59 263	647 383
Sex/age						
Female						
18 - 34	102	73	2004	1286	349	3813
35 - 49	1736	1244	34 253	21 972	5966	65 172
50 - 64	14 070	10 083	277 579	178 055	48 347	528 133
65 - 74	8926	6396	176 094	112 957	30 671	335 045
≥ 75	13 811	9897	272 477	174 782	47 458	518 426
Male						
18 - 34	18	13	364	234	63	693

AU = Australia and New Zealand; CA = Canada; EU = European Union, European Economic Area, and Switzerland; Other = emerging markets in Asia, Africa, Middle East, and Latin America where Amgen is the marketing authorization holder; US = United States
Note: Numbers may not add to the total due to rounding. Cumulative data to 26 September 2019
[a] Age and sex breakdowns are based on patient characteristics in MarketScan, a US health insurance claims database. Applying these distributions to regions outside the United States requires strong assumptions that are not easily testable.
[b] Does not include Japan. Does not include product distributed in China through BeiGene

Postauthorization Use From Business Partners

Table 16 reports postmarketing patient-years of exposure accrued in territories served by Amgen's business partners Daiichi Sankyo, GlaxoSmithKline, and BeiGene. These estimates were calculated based on data reported to Amgen by Amgen's business partners.

Table 16. Patient-years of Postmarketing Exposure Accrued by Business Partners

Company	Product	Cumulative Since Launch
Daiichi Sankyo	Denosumab (RANMARK)	202 071
BeiGene	Denosumab (XGEVA)	239
GlaxoSmithKline[a]	Denosumab (XGEVA)	11 542
	Subtotal	213 852

[a] No denosumab (XGEVA) data available after June 2018 in GlaxoSmithKline territories; the last denosumab (XGEVA) country license held by GlaxoSmithKline was cancelled on 06 June 2019. All country licenses were transferred back to Amgen from GlaxoSmithKline; therefore, there is no reorting period exposure and only cumulative data has been presented.

Table 17 reports the total postmarketing patient-years of exposure accrued worldwide in Amgen territories and in territories served by business partners.

Table 17. Patient-years of Postmarketing Exposure Worldwide in All Territories

Product	Cumulative Since Launch
Denosumab (RANMARK, XGEVA)	1 547 151

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

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

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

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

Table 18. New or Reclassification of Safety Concerns in the RMP

Safety Concern	Action Taken	Justification
Removal of Safety Concerns from the RMP		
Important Potential Risks		
Infection	Infections, previously classified as an important potential risk, has been removed from the list of safety concerns.	Changes in the level of scientific evidence for the causal association or risk-benefit impact: Accumulated clinical and postmarketing data do not support the initial supposition of a potential causal association between infections and XGEVA (denosumab). An observational study reviewing infections leading to hospitalizations did not identify an increased risk of infection. The incidence rates (95% CI) of infection leading to hospitalization per 100 person-years were 17.3 (15.7, 19.1) in the XGEVA inception cohort, 16.8 (15.0, 18.8) in the zoledronic acid inception cohort, and 16.7 (13.6, 20.4) in the XGEVA-switch cohort. Additionally, subsequent interval and cumulative assessments of clinical trials and postmarketing data, as summarized in the annual Periodic Safety Update Report (PSUR)/Periodic Benefit Risk Evaluation Reports (PBRERs), have not identified new safety information. There are no additional pharmacovigilance or risk minimization activities ongoing or planned to further characterize this risk.
Osteonecrosis Outside the Jaw Including External Auditory Canal	Osteonecrosis Outside the Jaw Including External Auditory Canal, previously classified as an important potential risk, has been removed from the list of safety concerns.	Changes in the level of scientific evidence for the causal association or risk-benefit impact: Accumulated clinical and postmarketing data do not support the initial supposition of a potential causal association between osteonecrosis outside the jaw including external auditory canal and XGEVA (denosumab). Subsequent interval and cumulative assessments of clinical trials and postmarketing data, as summarized in the annual PSUR/PBRERs, have not identified new safety information. The overall reporting rate in clinical trial and postmarketing settings of osteonecrosis outside the jaw including external auditory canal have been very low.

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

Table 18. New or Reclassification of Safety Concerns in the RMP

Safety Concern	Action Taken	Justification
Removal of Safety Concerns from the RMP (continued)		
Important Potential Risks (continued)		
Osteonecrosis Outside the Jaw Including External Auditory Canal		Events of osteonecrosis outside the jaw (avascular necrosis) observed in the SRE clinical program have been rare, and the frequency of these events in the GCTB study was uncommon. The cumulative reporting rate in the postmarketing setting of osteonecrosis outside the jaw through 26 August 2020 is 90 per 1 527 988 patient-years or 5.89 per 100 000 patient years. The cumulative reporting rate in the postmarketing setting of osteonecrosis of the external auditory canal through 26 August 2020 is 3 per 1 527 988 patient-years or 0.20 per 100 000 patient years. There are currently no additional pharmacovigilance or risk minimization activities ongoing or planned to further characterize this risk.
Missing Information		
Immunogenicity following a significant change to the manufacturing process	Immunogenicity following a significant change to the manufacturing process, previously classified as missing information, has been removed from the list of safety concerns.	Changes in the level of scientific evidence: Accumulated clinical and postmarketing data do not indicate any evidence of enhanced immunogenicity following the manufacturing change from CP2 to CP4. Subsequent interval and cumulative assessments of clinical trials and postmarketing data, as summarized in the annual PSUR/PBRERs, have not identified any safety concerns related to the manufacturing change. Antidenosumab antibody testing has been performed in the clinical trial and postmarketing setting. The incidence of antibody development remains low in clinical trials and no cases of antibody development have occurred in the postmarketing setting. Since the marketing application, the incidence of antibody development remains low (13 of 5282 subjects) in XGEVA clinical studies. The antibodies detected were transient and non neutralizing. Amgen has tested 4 postmarketing samples (from a single patient at 4 different time points) since the approval of denosumab (XGEVA), and all samples were negative for antidenosumab binding antibodies.

GCTB = giant cell tumor of bone; PBRER = Periodic Benefit Risk Evaluation Report; PSUR = Periodic Safety Update Report; SmPC = Summary of Product Characteristics; SRE = skeletal related events

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 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 randomized, controlled, phase 3 clinical trials. This risk was further supported by postmarketing reports.
Characterization of the risk	
Frequency	In the pooled pivotal SRE Solid Tumor studies, the subject incidence of positively adjudicated adverse events of ONJ was 1.8% in the denosumab group and 1.3% in the zoledronic acid group; the hazard ratio was 1.38 (95% CI: 0.91, 2.11). In the SRE multiple myeloma study, the subject incidence of positively adjudicated adverse events of ONJ was 4.1% in the denosumab group and 2.8% in the zoledronic acid group; the hazard ratio was 1.47 (95% CI: 0.88, 2.48). In clinical trials, the incidence of ONJ was higher with longer duration of exposure (XGEVA® SmPC, May 2018). In Study 20101363, a non-interventional postmarketing observational study of 2877 patients with cancer treated with XGEVA or zoledronic acid for SRE prevention, the incidence rates (95% CI) of medically confirmed ONJ per 100 person-years were 3.0 (2.3, 3.7) in the XGEVA inception cohort, 1.0 (0.6, 1.5) in the zoledronic acid inception cohort, and 4.3 (2.8, 6.3) in the XGEVA-switch cohort (this cohort included patients who switched to XGEVA after having started antiresorptive therapy with bisphosphonates for SRE prevention of no more than 2 years' net duration).
Severity	Most events leading to adjudication as ONJ were assessed as moderate to severe. Life-threatening events have been reported.
Reversibility	In general, ONJ events are clinically reversible. The majority of ONJ cases resolve with denosumab treatment interruption or discontinuation. Surgical treatment may be required; bone resection is not usually necessary.
Long-term outcomes	No data on long-term outcomes are available.

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

Table 19. Important Identified Risk: Osteonecrosis of the Jaw

Characterization of the risk (continued)	
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 associated with ONJ include the use of antiresorptives (particularly aminobisphosphonates delivered by intravenous [IV] dosing), older age, poor dental hygiene, periodontal disease, invasive dental procedures, trauma from poorly fitting dentures, malignancy, chemotherapy (including antiangiogenesis agents such as bevacizumab), radiation to head and neck, corticosteroids, hypercoagulable state secondary to underlying malignancy, smoking and vascular insufficiency due to thrombosis (Almazrooa and Woo, *J Amer Dental Assoc*, 2009; 140:864-875; Estilo et al, *J Clin Oncol*, 2008; 26:4037-4038; Mehrotra and Ruggiero, *Hematol*, 2006; 2006:356-360; Ruggiero et al, *J Oncol Pract*, 2006; 2:7-14).
Preventability	A dental examination with appropriate preventive dentistry is recommended prior to treatment with XGEVA, 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 XGEVA should receive care by a dentist or an oral surgeon. In patients who develop ONJ during treatment with XGEVA, a temporary interruption of treatment should be considered based on individual risk/benefit assessment until the condition resolves. Good oral hygiene practices should be maintained during treatment with XGEVA and dental health should be monitored.
Impact on the risk-benefit balance of the product	The risk of ONJ events has been considered in the product benefit-risk assessment. In light of the product labeling and a patient reminder card that has been proposed to minimize this risk, the overall benefit-risk balance is considered to be positive.
Public health impact	Significant public health impact is not expected based on the relative frequency observed in clinical trials and with the observations that most ONJ events appear to be moderate to severe in severity and resolve without requiring extensive surgical treatment.

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IV = intravenous; ONJ = osteonecrosis of the jaw; SRE = skeletal-related event; SmPC = Summary of Product Characteristics

Table 20. 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 causes of AFF are likely multifactorial. Based on nonclinical studies of bisphosphonates, 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 randomized, controlled, phase 3 clinical trials and in open-label, phase 2 clinical trials. This risk was further supported by postmarketing reports.
Characterization of the risk	
Frequency	In a comprehensive evaluation of denosumab 120 mg clinical trials, 15 subjects experienced 17 events meeting the American Society for Bone and Mineral Research criteria for AFF. This corresponds to 0.2% (15 of 8342) of all subjects who received at least 1 dose of denosumab (Similar results are observed when consideration is limited to studies utilizing monthly dosing throughout [0.1%, 6 subjects with AFF in 6101 subjects]). All of these adjudicated events of AFF occurred in subjects who received denosumab 120 mg for at least 4 years corresponding to 0.7% (15 of the 2228) of subjects who were followed for 4 or more years. In the clinical trial program, AFF has been reported uncommonly in patients treated with XGEVA 120 mg and the risk increased with longer duration of treatment. Events have occurred during treatment and up to 9 months after treatment was discontinued.
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.
Reversibility	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 hip 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 et al, 2016; Unnanuntana et al, 2013).

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

Table 20. Important Identified Risk: Atypical Femoral Fracture

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, *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 [RA], hypophosphatasia) and with use of bisphosphonates, glucocorticoids, and proton pump inhibitors (Shane et al, *J Bone Miner Res*, 2010; 25:2267-2294).
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 AFF events has been considered in the product benefit-risk assessment. In light of the product labeling that has been proposed to minimize this risk, the overall benefit-risk balance is considered to be positive.
Public health impact	Based on the frequency of AFF, the size of the indicated populations, and usage patterns of denosumab in clinical practice, no significant additional public health impact is expected.

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AFF = atypical femoral fracture; RA = rheumatoid arthritis

Table 21. Important Identified Risk: Hypercalcemia Several Months After the Last Dose in Patients With Giant Cell Tumor of Bone and in Patients With Growing Skeletons

Potential mechanisms	The mechanism(s) of hypercalcemia several months after the last dose of denosumab in patients with GCTB and in patients with a growing skeleton are not well characterized, but may be a consequence of the following, alone, or in combination: Denosumab treatment and resultant RANK/RANKL pathway inhibition in adults with giant-cell containing lesions such as GCTB leads to histopathologic evidence of a dramatic decrease in osteoclast-like giant cells which is complemented by woven bone formation and calcification within the tumors and even at sites of distant metastases (Ghermandi et al, 2016; Yamagishi et al, 2016; Branstetter et al, 2012). It is possible this calcium could serve as a depot that is mobilized with reactivation of tumor-associated, RANKL driven giant cell mediated osteolysis following cessation of XGEVA. • Hypercalcemia may result from rapid resorption of retained primary spongiosa in a skeleton with active endochondral ossification such as in patients with a growing skeleton. 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 the skeleton either near the growth plates (as can be the case with the young adult and adolescent patients) or from the giant cell tumors themselves that have partially ossified in the cases of the adult patients with tumor recurrence via an autocrine/paracrine mechanism (Cowan et al, 2011). • The magnitude of the resorptive response following treatment withdrawal in the patients with GCTB and in those with an immature skeleton could be dictated by the normal high rate of bone turnover within the GCTB lesion or in the growing skeleton of young patients. The response of the osteoclast lineage to loss of inhibition of osteoclastogenesis may be intrinsically more robust in young individuals or may be affected by intratumor signaling pathways (eg, parathyroid hormone-related protein) in GCTB.
Evidence source(s) and strength of evidence	This risk was identified in phase 2 clinical trials of adolescent and adult patients with GCTB, and in postmarketing reports of pediatric patients using denosumab for unauthorized indications.
Characterization of the risk	
Frequency	Based on the 4 relevant clinical trial case reports (2 adults and 2 adolescents) identified from the completed Amgen clinical Study 20062004 of subjects with GCTB (526 subjects having received at least 1 dose of XGEVA), the frequency of hypercalcemia in patients with GCTB following discontinuation of XGEVA is 0.8 events per 100 subjects which corresponds to an uncommon frequency (≥ 0.1 and < 1 event per 100 subjects).

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

Table 21. Important Identified Risk: Hypercalcemia Several Months After the Last Dose in Patients With Giant Cell Tumor of Bone and in Patients With Growing Skeletons

Characterization of the risk (continued)	
Frequency (continued)	In addition, clinically significant cases of post-treatment hypercalcemia have been identified from literature case reports of denosumab use in pediatric patients for unapproved indications such as fibrous dysplasia, aneurysmal bone cysts, and juvenile Paget's disease.
Severity	In the GCTB study, the events of hypercalcemia in the 4 subjects from Study 20062004 were considered grade 2, 3, or 4 in severity. All subjects had acute renal injury and all were hospitalized. Three of 4 subjects had more than 1 event. The severity of the events in the postmarketing literature case reports appears qualitatively similar.
Reversibility	Hypercalcemia is reversible with appropriate supportive therapy.
Long-term outcomes	No data on long-term outcomes are available.
Impact on quality of life	Patients may present with severe hypercalcemia requiring hospitalization. Patients who experience hypercalcemia may develop complications such as acute renal injury.
Risk factors and risk groups	Patients with GCTB and young patients with growing skeletons following discontinuation of XGEVA. In general, the most common cause of hypercalcemia in humans is hyperparathyroidism, particularly among women and individuals aged 65 years or older (Minisola et al, *BMJ*, 2015;350:h2723). Hyperthyroidism and rhabdomyolysis associated with renal failure also increase the risk of hypercalcemia, as does the ingestion of large of amounts of calcium through dairy products or more recently liberal use of calcium supplements (Machado et al, *J Clin Med*, 2015; 4:414-424; Minisola et al, *BMJ*, 2015;350:h2723).
Preventability	No preventive measures are known. Monitor patients for signs and symptoms of hypercalcemia and treat appropriately. Periodic serum calcium assessments should be given to at-risk patients as clinically indicated. The need for calcium and vitamin D supplementation should be reassessed if denosumab is discontinued.
Impact on the risk-benefit balance of the product	The risk of hypercalcemia events several months after the last dose in patients with GCTB and in patients with growing skeletons has been considered in the product benefit-risk assessment. In light of the product labeling that has been proposed to minimize this risk, the overall benefit-risk balance is considered to be positive.
Public health impact	No significant public health impact is expected as hypercalcemia several months after the last dose in patients with GCTB occurs uncommonly and GCTB is a rare tumor. Off-label use of denosumab in pediatric patients appears to be limited to rare conditions for which there is significant unmet medical need.

GCTB = giant cell tumor of bone; RANK = receptor activator of nuclear factor kappa-B; RANKL = RANK ligand

Table 22. Important Potential Risk: Cardiovascular Events

Potential mechanisms	Elevated levels of osteoprotegerin (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	The risk of CV events is a regulatory concern based on the epidemiological association between OPG levels and CV disease in man. Clinical data have not substantiated a cause-and-effect between OPG and atherosclerotic processes nor between denosumab or inhibition of RANKL and undesirable CV outcomes.
Characterization of the risk	
Frequency	In the pooled pivotal SRE Solid Tumor studies, subject incidence of CV adverse events was 29.7% in both treatment groups; the hazard ratio was 0.98 (95% CI: 0.89, 1.08). In a pivotal study with denosumab 120 mg Q4W in subjects with CRPC (Study 20050147), the subject incidence of CV adverse events was 33.1% in the denosumab group and 27.0% in the placebo group; the hazard ratio was 1.23 (95% CI: 1.02, 1.49). In the SRE multiple myeloma study, the subject incidence of adverse events of cardiac disorders was 11.6% in the denosumab group and 13.5% in the zoledronic acid group; the hazard ratio was 0.85 (95% CI: 0.65, 1.12). The subject incidence of adverse events of vascular disorder was 20.9% in the denosumab group and 19.8% in the zoledronic acid group; the hazard ratio was 1.07 (95% CI: 0.86, 1.31).
Severity	The majority of CV events were mild to moderate. Life-threatening and fatal events have been reported.
Reversibility	No data on reversibility are available.
Long-term outcomes	No data on long-term outcomes are available.
Impact on quality of life	Cardiovascular disease varies greatly in severity. For severe disease, patients may be hospitalized for treatment and disability may occur.
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 CV conditions and, thus, a higher incidence of CV 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).

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

Table 22. Important Potential Risk: Cardiovascular Events

Risk factors and risk groups (continued)	Risk factors for atherosclerosis include age, gender, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes, and concomitant medications, including antipsychotic agents and cyclooxygenase-2 (COX-2) inhibitors (Murphy and Dargie, *Drug Safety*, 2007; 30(9):783-804; Smith et al, *Circulation*, 2004; 109(21):2613-2616).
Preventability	Based on clinical data to date, denosumab has not been associated with an increased incidence or severity of CV adverse effects; therefore, no preventive measures are defined. Patients with potential CV events should be managed according to usual standards of care.
Impact on the risk-benefit balance of the product	The risk of CV events has been considered in the product benefit-risk assessment, and the overall benefit-risk balance is considered to be positive.
Public health impact	Significant public health impact on CV disease severity or incidence is not expected based on the information from denosumab clinical studies in the advanced cancer and postmenopausal osteoporosis (PMO)/hormone ablation therapy (HALT) settings.

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COX-2 = cyclooxygenase-2; CV = cardiovascular; CRPC = castrate-resistant prostate cancer; HALT = hormone ablation therapy; OPG = osteoprotegerin; PMO = postmenopausal osteoporosis; Q4W = every 4 weeks; RANKL = RANK ligand; SRE = skeletal-related event

Table 23. Important Potential Risk: Malignancy

Potential mechanisms	The risk of malignancy is a theoretical concern that RANKL inhibition may lead to an increased risk for a new primary malignancy (NPM) by impairing immune surveillance mechanisms.
Evidence source(s) and strength of evidence	Imbalance is observed in the NPM events between the zoledronic acid and XGEVA treatment groups in the pivotal clinical studies. The results of Study 20170728, a postmarketing retrospective cohort study, showed NPM incidence rates for XGEVA were generally lower than those for zoledronic acid in unadjusted analyses, suggesting no obvious excess risk associated with XGEVA.
Characterization of the risk	
Frequency	In the primary, double-blind treatment phases of 4 phase 3 active-controlled clinical trials in patients with advanced malignancies involving bone, NPM was reported in 54/3691 (1.5%) of patients treated with XGEVA (median exposure of 13.8 months; range: 1.0 to 51.7) and 33/3688 (0.9%) of patients treated with zoledronic acid (median exposure of 12.9 months; range: 1.0 to 50.8). The cumulative incidence at 1 year was 1.1% for denosumab and 0.6% for zoledronic acid, respectively. In the SRE multiple myeloma study, the subject incidence of adverse events of NPM was 2.6% in the denosumab group and 1.4% in the zoledronic acid group; the hazard ratio was 1.81 (95% CI: 0.90, 3.66). Subjects who had new malignancies in this study generally had underlying risk factors for malignancy and no pattern was apparent in the types of new primary malignancies. In clinical Study 20062004 in GCTB, based on medical review and a data cut-off date of the final analysis of 15 August 2018, a total of 20 subjects (3.8%; N = 526) developed new malignancy in GCTB. Of these 20 subjects, 9 subjects developed new malignancies that were unrelated to GCTB: 2 events (0.4%) of ductal breast carcinoma and single events of each, adenocarcinoma of colon, breast cancer stage I, neoplasm, oesophageal adenocarcinoma, osteosarcoma, papillary thyroid cancer, renal cancer, rhabdomyosarcoma, and thyroid cancer. A total of 11 subjects (2.1%) developed new malignancy in GCTB: 5 subjects were deemed to have had primary malignant GCTB, 5 subjects were assessed to have had sarcomatous transformation, and 1 subject had secondary malignant GCTB (post-radiation). In Study 20170728, a retrospective observational cohort study of 9710 patients with bone metastases from breast, prostate, or lung cancer treated with XGEVA or IV zoledronic acid, the overall rate of NPM for the breast cancer cohort was 11.5 per 1000 person-years of follow-up (PY) in the XGEVA group and 16.2 per 1000 PY in the zoledronic acid group; for the prostate cancer cohort was 19.6 per 1000 PY in the XGEVA group and 20.1 per 1000 PY in the zoledronic acid group; and for the lung cancer cohort was 9.5 per 1000 PY in the XGEVA group and 11.5 per 1000 PY in the zoledronic acid group.

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

Table 23. Important Potential Risk: Malignancy

Characterization of the risk (continued)	
Frequency (continued)	The 3-year cumulative incidence of NPM for the breast cancer cohort was 0.022 (95% CI: 0.014, 0.035) in the XGEVA group and 0.032 (95% CI: 0.023, 0.045) in the zoledronic acid group; for the prostate cancer cohort was 0.034 (95% CI: 0.026, 0.044) in the XGEVA group and 0.036 (95% CI: 0.026, 0.049) in the zoledronic acid group; and for the lung cancer cohort was 0.007 (95% CI: 0.004, 0.012) in the XGEVA group and 0.008 (95% CI: 0.005, 0.014) in the zoledronic acid group.
Severity	Not applicable.
Reversibility	No data on reversibility are available.
Long-term outcomes	No data on long-term outcomes are available.
Impact on quality of life	Malignancy is typically disabling and may require surgery, chemotherapy, and/or radiotherapy.
Risk factors and risk groups	General factors for increasing risk of NPM include advancing age, diet, cigarette smoking, excessive ethanol consumption, and numerous environmental toxins. In addition, advanced cancer populations are at increased risk for NPM because of their existing malignancy, possible genetic predisposition, and exposure to chemotherapy and radiation treatment.
Preventability	Second malignant neoplasms have become increasingly recognized and current recommendations include vigilance for these cancers in adult cancer survivors.
Impact on the risk-benefit balance of the product	The risk of malignancy events has been considered in the product benefit-risk assessment. In light of the product labeling that has been proposed to minimize this risk, the overall benefit-risk balance is considered to be positive.
Public health impact	Significant public health impact is not expected based on the information from studies in the PMO/HALT and advanced cancer settings.

GCTB = giant cell tumor of bone; HALT = hormone ablation therapy; IV = intravenous; NPM = new primary malignancy; PMO = postmenopausal osteoporosis; PY = person-years of follow-up; RANKL = RANK ligand; SRE = skeletal-related event

Table 24. Important Potential Risk: Delay in Diagnosis of Primary Malignancy in Giant Cell Tumor of Bone

Potential mechanisms	Due to well described sampling error at the time of GCTB diagnosis, primary malignancy in giant cell tumor of bone (PMGCTB) may be missed and benign GCTB may be presumed. Based on the mechanism of action and pathology of GCTB, denosumab is only expected to treat benign GCTB. However there was a theoretical concern that treatment of an undiagnosed PMGCTB with denosumab could delay the diagnosis of PMGCTB.
Evidence source(s) and strength of evidence	The risk of delay in diagnosis of PMGCTB is a regulatory concern based on the difficulties in diagnosing PMGCTB in Study 20062004.
Characterization of the risk	
Frequency	In clinical studies in GCTB, based on medical review, 11 subjects (2.1%; N = 523) had GCTB bone malignancies. Of these, 5 subjects (1.0%) had PMGCTB.

	Time to PMGCTB
Number of cases	5
Mean time (Q1, Q3) to malignancy (months)[a]	19.12 (11.99, 24.18)
Median (min, max) denosumab exposure (months)	8.44 (2.8, 14.8)

[a] Time from diagnosis of GCTB to diagnosis of malignancy of GCTB

Source: Table GCTB Table 200-6.21.06

Severity	Not applicable.
Reversibility	Not applicable.
Long-term outcomes	No data on long-term outcomes are available.
Impact on quality of life	Malignancy is typically disabling and may require surgery, chemotherapy, and/or radiotherapy.
Risk factors and risk groups	Patients with GCTB are known to be at risk for PMGCTB.
Preventability	No preventive measures are known.
Impact on the risk-benefit balance of the product	The risk of delay in diagnosis of PMGCTB events has been considered in the product benefit-risk assessment. In light of the product labeling that has been proposed to minimize this risk, the overall benefit-risk balance is considered to be positive.
Public health impact	Given that GCTB is very rare condition, no impact on public health is expected.

GCTB = giant cell tumor of bone; PMGCTB = primary malignant giant cell tumor of bone

Table 25. Important Potential Risk: Hypercalcemia Several Months After the Last Dose in Patients Other Than Those With Giant Cell Tumor of Bone or Growing Skeletons

Potential mechanisms	The pathogenesis of hypercalcemia several months after the last dose in patients other than those with GCTB or growing skeletons may be a consequence of the transient increase in bone turnover activity. Upon cessation of denosumab, the disinhibition of RANKL allows for terminal differentiation and activation of osteoclasts, which were suppressed during treatment. In patients with underlying causes for calcium dyscrasias (ie, subclinical hyperparathyroidism), denosumab discontinuation, with its transient increase in bone remodeling and accompanying release of bone mineral, could theoretically be associated with transient hypercalcemia in susceptible individuals if the normal homeostatic mechanism regulating serum calcium are not appropriately maintained.
Evidence source(s) and strength of evidence	Hypercalcemia several months after the last dose in patients other than those with GCTB or growing skeletons is a theoretical concern based on the identified risk in other specific populations, GCTB, and pediatric populations.
Characterization of the risk	
Frequency	Cases of hypercalcemia in the off treatment period have been reported in clinical studies, but given the disease state of the subjects, as well as other confounding factors, the occurrence of hypercalcemia in patients other than those with GCTB or with growing skeletons cannot be attributed to discontinuation of XGEVA based on available information. As the mechanism for the identified risk in the susceptible populations is not well understood, a theoretical risk remains in other patient groups.
Severity	Not applicable.
Reversibility	No data on reversibility are available.
Long-term outcomes	No data on long-term outcomes are available.
Impact on quality of life	Patients may present with severe hypercalcemia requiring hospitalization. Patients who experience hypercalcemia may develop complications such as acute renal injury.
Risk factors and risk groups	Patients other than those with GCTB or growing skeletons following cessation of XGEVA.
Preventability	No preventive measures are known.
Impact on the risk-benefit balance of the product	The risk of hypercalcemia events following treatment discontinuation in patients other than those with GCTB or growing skeletons has been incorporated in the product benefit-risk assessment, and the overall benefit-risk balance remains positive.
Public health impact	No significant public health impact is expected as the potential events remain infrequent despite extensive market exposure.

GCTB = giant cell tumor of bone; RANKL = RANK ligand

SVII.3.2 Presentation of the Missing Information

Table 26. Missing Information: Use in Patients With Prior Intravenous Bisphosphonate Treatment

Evidence source	The incidence of ONJ in patients with prior IV bisphosphonate use was similar to that of patients who only received XGEVA in the completed Study 20101363. No notable association was evident between ONJ and prior use of bisphosphonates.
Population in need of further characterization	There is information from studies in patients with cancer showing that there is no increased risk of serious complications caused by bone metastases in patients who received XGEVA following treatment with bisphosphonates. However, more information is needed.

Table 27. Missing Information: Safety With Long-term Treatment and With Long-term Follow-up After Treatment in Adults and Skeletally Mature Adolescents With GCTB

Evidence source	The overall safety profile of XGEVA in the completed Study 20062004 was similar to the safety profile of XGEVA observed in the treatment of subjects with advanced cancer and bone metastases.
Population in need of further characterization	Information on safety with long-term treatment and with long-term follow-up in adults or adolescents with GCTB will be monitored by routine pharmacovigilance activities.

Table 28. Missing Information: Off-label Use in Patients With GCTB That is Resectable Where Resection is Unlikely to Result in Severe Morbidity

Evidence source	No formal studies have been completed to determine XGEVA's effect on off-label use in patients with GCTB that is resectable where resection is unlikely to result in severe morbidity.
Population in need of further characterization	Information is not available on safety in patients with GCTB that is resectable where resection is unlikely to result in severe morbidity.

Part II: Module SVIII - Summary of the Safety Concerns

Table 29. Summary of Safety Concerns

Important identified risks	• Osteonecrosis of the jaw • Atypical femoral fracture • Hypercalcemia several months after the last dose in patients with giant cell tumor of bone and in patients with growing skeletons
Important potential risks	• Cardiovascular events • Malignancy • Delay in diagnosis of primary malignancy in giant cell tumor of bone • Hypercalcemia several months after the last dose in patients other than those with giant cell tumor of bone or growing skeletons
Missing information	• Patients with prior intravenous bisphosphonate treatment • Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumor of bone • Off-label use in patients with giant cell tumor of bone that is resectable where resection is unlikely to result in severe morbidity

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 30 and Table 31.

Table 30. Specific Adverse Reaction Follow-up Questionnaires

Follow-up Questionnaire (Annex 4. Specific Adverse Drug Reaction Follow-up Forms)	Safety Concern(s)	Purpose
Potential Osteonecrosis of the Jaw	Osteonecrosis of the Jaw	To monitor the reporting rate and nature of ONJ in patients treated with XGEVA in the postmarketing environment.
Potential atypical fracture	Atypical femoral fracture	To monitor the reporting rate and nature of AFF in patients treated with XGEVA in the postmarketing environment.

Table 31. Other Forms of Routine Pharmacovigilance Activities

Description of Activity	Safety Concern(s)	Objectives	Milestones
Potential events of ONJ, reported in ongoing clinical trials, are adjudicated by a panel of external medical experts.	Osteonecrosis of the Jaw	To collect further information on rate of ONJ in clinical studies.	Not applicable
Potential events of ONJ reported in the postmarketing setting are medically reviewed internally to determine if the ONJ events meet the American Association of Oral and Maxillofacial Surgeons (AAOMS) ONJ case definition.	Osteonecrosis of the Jaw	To monitor the reporting rate and nature of ONJ in patients treated with XGEVA in the postmarketing environment.	Not applicable
Potential cases of AFF from clinical trial setting are adjudicated by an independent committee that is blinded to treatment.	Atypical Femoral Fracture	To collect further information on rate of AFF in clinical studies.	Not applicable
Potential cases of AFF from postmarketing setting are medically reviewed internally based on diagnosis of the radiographic findings and without requiring the radiographs to be sent to Amgen.	Atypical Femoral Fracture	To monitor reporting rate and nature of AFF in patients treated with XGEVA in the postmarketing environment.	Not applicable
Case-series, prospective follow-up study of positively adjudicated ONJ cases in Study 20101102 is being conducted to collect information on frequency of risk factors for ONJ (including prior IV bisphosphonate use).	Patients With Prior Intravenous Bisphosphonate Treatment	To collect information on frequency of risk factors for ONJ (including prior IV bisphosphonate use).	Not applicable

III.2 Additional Pharmacovigilance Activities

Table 32. Category 1 to 3 Postauthorization Safety Studies

Study Short Name, Study Title and Category Number	Rationale and Study Objectives	Study Design	Study Population	Milestones
Postmarketing case registry study Study 20101102 Osteonecrosis of the jaw (ONJ) case registry Category 3	Primary objective: • To estimate the rate and describe the time course of resolution of ONJ. Safety concerns addressed: • Osteonecrosis of the jaw • Patients with prior intravenous bisphosphonate treatment	Observational registry	Subjects ≥ 18 years of age with diagnosis of cancer who have positively-adjudicated, newly diagnosed ONJ	Protocol submission: June 2010 Study status: Ongoing Final report: Anticipated Q4 2021

[redacted]

Table 32. Category 1 to 3 Postauthorization Safety Studies

Study Short Name, Study Title and Category Number	Rationale and Study Objectives	Study Design	Study Population	Milestones
Long-term safety follow-up study Study 20140114 Long-term safety follow-up of subjects with giant cell tumor of bone treated with denosumab in Study 20062004 Category 3	Primary objective: • Evaluate adverse events of interest in subjects with GCTB treated with denosumab in Study 20062004. Secondary objectives: • Evaluate treatment-emergent adverse events for subjects who are receiving denosumab; • Evaluate serious adverse events for all subjects; • Summarize the rate of disease progression or recurrence of GCTB for all subjects; and • Summarize the use of GCTB interventions for all subjects. Safety concerns addressed: • Osteonecrosis of the jaw • Atypical femoral fracture • Delay in diagnosis of primary malignancy in giant cell tumor of bone • Malignancy • Hypercalcemia several months after the last dose in patients with giant cell tumor of bone and in patients with growing skeletons	Prospective study to provide long-term safety follow-up for subjects who complete Study 20062004	Subjects with GCTB who were previously treated with denosumab in Study 20062004	Protocol submission: May 2014 Study status: Ongoing Final report: Anticipated Q4 2023

III.3 Summary Table of Additional Pharmacovigilance Activities

There are no ongoing or planned XGEVA category 1 or 2 studies.

Table 33. (Table Part III.1) Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required additional pharmacovigilance activities				
Postmarketing case registry study Study 20101102 Osteonecrosis of the jaw (ONJ) case registry Ongoing	Primary objective: • To estimate the rate and describe the time course of resolution of ONJ.	• Osteonecrosis of the jaw • Patients with prior intravenous bisphosphonate treatment	Protocol Submission Final report	June 2010 Anticipated Q4 2021
Long-term safety follow-up study Study 20140114 Long-term safety follow-up of subjects with giant cell tumor of bone treated with denosumab in Study 20062004 Ongoing	Primary objective: • Evaluate adverse events of interest in subjects with GCTB treated with denosumab in Study 20062004. Secondary objectives: • Evaluate treatment-emergent adverse events for subjects who are receiving denosumab; • Evaluate serious adverse events for all subjects; • Summarize the rate of disease progression or recurrence of GCTB for all subjects; and • Summarize the use of GCTB interventions for all subjects.	• Osteonecrosis of the jaw • Atypical femoral fracture • Delay in diagnosis of primary malignancy in giant cell tumor of bone • Malignancy • Hypercalcemia several months after the last dose in patients with giant cell tumor of bone and in patients with growing skeletons	Protocol Submission Final report	May 2014 Anticipated Q4 2023

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 34. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Identified Risks	
Osteonecrosis of the jaw	Routine risk communication: • SmPC Section 4.3 • SmPC Section 4.4 • SmPC Section 4.8 • SmPC Section 5.1 • PIL Section 2 • PIL Section 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendations for oral examination, maintenance of good oral hygiene during treatment, management of patients with unavoidable invasive dental procedure, and temporary interruption of treatment if ONJ occurs are included in Section 4.4 of SmPC. Other risk minimization measures beyond the PI: • Legal status: XGEVA is a medicinal product subject to restricted medical prescription.
Atypical femoral fracture	Routine risk communication: • SmPC Section 4.4 • SmPC Section 4.8 • PIL Section 2 • PIL Section 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 Section 4.4 of SmPC. Other risk minimization measures beyond the PI: • Legal status: XGEVA is a medicinal product subject to restricted medical prescription.

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

Table 34. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Identified Risks (continued)	
Hypercalcemia several months after the last dose in patients with giant cell tumor of bone and in patients with growing skeletons	Routine risk communication: • SmPC Section 4.4 • SmPC Section 4.8 • PIL Section 2 • PIL Section 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendations for monitoring the patients for signs and symptoms of hypercalcaemia after discontinuation of XGEVA treatment are included in Section 4.4 of SmPC and Section 4 of the PIL. Other risk minimization measures beyond the PI: • Legal status: XGEVA is a medicinal product subject to restricted medical prescription.
Important Potential Risks	
Cardiovascular events	Routine risk communication: • Not applicable Other risk minimization measures beyond the PI: • Legal status: XGEVA is a medicinal product subject to restricted medical prescription.
Malignancy	Routine risk communication: • SmPC Section 4.4 • SmPC Section 4.8 • SmPC Section 5.1 • PIL Section 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendations for monitoring the patients for radiological signs of malignancy, new malignancy, or osteolysis are included in Section 4.4 of SmPC. Other risk minimization measures beyond the PI: • Legal status: XGEVA is a medicinal product subject to restricted medical prescription.

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

Table 34. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Potential Risks (continued)	
Delay in diagnosis of primary malignancy in giant cell tumor of bone	Routine risk communication: • Not applicable Other risk minimization measures beyond the PI: • Legal status: XGEVA is a medicinal product subject to restricted medical prescription.
Hypercalemia several months after the last dose in patients other than those with GCTB or growing skeletons	Routine risk communication: • Not applicable Other risk minimization measures beyond the PI: • Legal status: XGEVA is a medicinal product subject to restricted medical prescription.
Missing Information	
Patients with previous intravenous treatment with bisphosphonate treatment	Routine risk communication: • SmPC Section 4.5 • SmPC Section 5.1 • PIL Section 2 Other risk minimization measures beyond the PI: • Legal status: XGEVA is a medicinal product subject to restricted medical prescription.
Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with GCTB	Routine risk communication: • Not applicable Other risk minimization measures beyond the PI: • Legal status: XGEVA is a medicinal product subject to restricted medical prescription.
Off-label use in patients with GCTB that is resectable where resection is unlikely to result in severe morbidity	Routine risk communication: • Not applicable Other risk minimization measures beyond the PI: • Legal status: XGEVA is a medicinal product subject to restricted medical prescription.

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GCTB = giant cell tumor of bone; ONJ = osteonecrosis of the jaw; PI = Product Information; PIL = Patient Information Leaflet; SmPC = Summary of Product Characteristics

V.2 Additional Risk Minimization Measures

Table 35. Additional Risk Minimization Measure: Patient Reminder Cards

Objectives	Patient Reminder Cards will be distributed to address the following risk: • Osteonecrosis of the jaw
Rationale for the additional risk minimization activity	The purpose of the Patient Reminder Cards is to remind patients about important safety information that they need to be aware of before and during treatment with denosumab (XGEVA®) injections for cancer-related conditions, including: • To tell their doctor/nurse if they have any problems with their mouth or teeth before starting treatment; • To maintain good oral hygiene and receive routine dental check-ups during treatment; • To inform their doctor and tell their dentist that they are being treated with denosumab (XGEVA) if they are under dental treatment or will undergo dental surgery; and • To contact their doctor and dentist immediately if they experience any problems with their mouth or teeth such as loose teeth, pain or swelling, non-healing of sores or discharge.
Target audience and planned distribution path	Target audience will be the patients. Patient reminder cards were distributed to prescribers with instructions to provide 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 PSURs. The distribution of the patient reminder card will be tracked to ensure that it was completed to the distribution 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. In addition, the focused questionnaire for postmarketing reports of ONJ presented in Annex 4. Specific Adverse Drug Reaction Follow-up Forms will be revised to permit inclusion of data on whether the patient affected by ONJ had previously received a patient reminder card or not.
Evaluation of the effectiveness of risk minimization activities	No change in risk benefit profile.
Removal of additional risk minimization activities (if applicable)	Not applicable.

EU = European Union; ONJ = osteonecrosis of the jaw; PSUR = Periodic Safety Update Report

V.3 Summary of Risk Minimization Measures

Table 36. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks		
Osteonecrosis of the jaw	Routine risk minimization measures: • SmPC Section 4.3 • SmPC Section 4.4, where recommendations for oral examination, maintenance of good oral hygiene, management of patients with unavoidable invasive dental procedure, and temporary interruption are discussed. • SmPC Section 4.8 • SmPC Section 5.1 • PIL Section 2, where recommendations for oral examination, maintenance of good oral hygiene, management of patients with unavoidable invasive dental procedure, and sign of ONJ are discussed. • PIL Section 4, where symptoms of ONJ is discussed. Additional risk minimization measures: • Patient reminder cards	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Denosumab core questionnaire – Osteonecrosis of the Jaw • Potential events of ONJ, reported in ongoing clinical trials, are adjudicated by a panel of external medical experts. • Potential events of ONJ reported in the postmarketing setting are medically reviewed internally to determine if the ONJ events meet the AAOMS ONJ case definition. Additional pharmacovigilance activities: • Study 20140114 • Study 20101102

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

Table 36. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks (continued)		
Atypical femoral fracture	Routine risk minimization measures: • SmPC Section 4.4, where recommendations for reporting new or unusual thigh, hip, or groin pain is discussed. • SmPC Section 4.8 • PIL Section 2, where recommendations for reporting new or unusual pain in you thigh, hip, or groin is discussed. • PIL Section 4, where signs of thigh bone fracture is discussed. Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Denosumab core questionnaire – Postmarketing reports of potential atypical fracture • Potential cases of AFF from clinical trial setting are adjudicated by an independent committee that is blinded to treatment. • Potential cases of AFF from postmarketing setting are medically reviewed internally based on diagnosis of the radiographic findings and without requiring the radiographs to be sent to Amgen. Additional pharmacovigilance activities: • Study 20140114
Hypercalcemia several months after the last dose in patients with giant cell tumor of bone and in patients with growing skeletons	Routine risk minimization measures: • SmPC Section 4.4, where recommendations for monitoring the patients for signs and symptoms of hypercalcaemia after discontinuation of XGEVA is discussed. • SmPC Section 4.8 • PIL Section 2, where recommendations for monitoring the patients for signs and symptorms of hypercalcemia after discontinuation of XGEVA treatment is discussed • PIL Section 4 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study 20140114

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

Table 36. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Potential Risks		
Cardiovascular events	No risk minimization measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Malignancy	Routine risk minimization measures: • SmPC Section 4.4, where recommendations for monitoring the patients for radiological signs of malignancy, new malignancy, or osteolysis is discussed. • SmPC Section 4.8 • SmPC Section 5.1 • PIL Section 4 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study 20140114
Delay in diagnosis of primary malignancy in giant cell tumor of bone	No risk minimization measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: Study 20140114
Hypercalemia several months after the last dose in patients other than those with GCTB or growing skeletons	No risk minimization measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: None

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

Table 36. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Missing Information		
Patients with previous intravenous treatment with bisphosphonate treatment	Routine risk minimization measures: • SmPC Section 4.5 • SmPC Section 5.1 • PIL Section 2 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study 20101102
Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with GCTB	No risk minimization measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Off-label use in patients with GCTB that is resectable where resection is unlikely to result in severe morbidity	No risk minimization measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: None

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AAOMS = American Association of Oral Maxillofacial Surgeons; AFF = atypical femoral fracture; GCTB = giant cell tumor of bone; ONJ = osteonecrosis of the jaw; PIL = patient information leaflet; SmPC = summary of product characteristics

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

A summary of the RMP for XGEVA is presented below.

Summary of Risk Management Plan for XGEVA® (Denosumab)

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

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

This summary of the RMP for XGEVA® 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 XGEVA®'s RMP.

I. The medicine and what it is used for

XGEVA® is authorized for prevention of skeletal-related events (pathological fracture, radiation to bone, spinal cord compression, or surgery to bone) in adults with advanced malignancies involving bone and for the treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity (see SmPC for the full indication). It contains denosumab as the active substance and it is given by subcutaneous administration.

Further information about the evaluation of XGEVA®'s benefits can be found in XGEVA®'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/XGEVA.

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

Important risks of XGEVA®, together with measures to minimize such risks and the proposed studies for learning more about XGEVA®'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 XGEVA®, 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 XGEVA® is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of XGEVA® 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 XGEVA®. 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 risks	• Osteonecrosis of the jaw • Atypical femoral fracture • Hypercalcemia several months after the last dose in patients with giant cell tumor of bone and in patients with growing skeletons
Important potential risks	• Cardiovascular events • Malignancy • Delay in diagnosis of primary malignancy in giant cell tumor of bone • Hypercalcemia several months after the last dose in patients other than those with giant cell tumor of bone or growing skeletons
Missing information	• Patients with prior intravenous bisphosphonate treatment • Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumor of bone • Off-label use in patients with giant cell tumor of bone that is resectable where resection is unlikely to result in severe morbidity

II.B. Summary of Important Risks

Important identified risk: Osteonecrosis of the Jaw	
Evidence for linking the risk to the medicine	This risk was identified in randomized, controlled, phase 3 clinical trials. This risk was further supported by postmarketing reports.
Risk factors and risk groups	Risk factors associated with osteonecrosis of the jaw (ONJ) include the use of antiresorptives (particularly aminobisphosphonates delivered by intravenous [IV] dosing), older age, poor dental hygiene, periodontal disease, invasive dental procedures, trauma from poorly fitting dentures, malignancy, chemotherapy (including antiangiogenesis agents such as bevacizumab), radiation to head and neck, corticosteroids, hypercoagulable state secondary to underlying malignancy, smoking and vascular insufficiency due to thrombosis (Almazrooa and Woo, *J Amer Dental Assoc*, 2009; 140:864-875; Estilo et al, *J Clin Oncol*, 2008; 26:4037-4038; Mehrotra and Ruggiero, *Hematol*, 2006; 2006:356-360; Ruggiero et al, *J Oncol Pract*, 2006; 2:7-14).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.3 • SmPC Section 4.4 • SmPC Section 4.8 • SmPC Section 5.1 • Patient Information Leaflet (PIL) Section 2 • PIL Section 4 Additional risk minimization measures: • Patient reminder cards
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 20140114 • Study 20101102 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 randomized, controlled, phase 3 clinical trials and in open-label, phase 2 clinical trials. This risk was further supported by postmarketing reports.
Risk factors and risk groups	Long-term antiresorptive treatment has been associated with atypical femoral fracture (AFF). Corticosteroids have also been reported in the literature to potentially be associated with AFF (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 [RA], 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 • SmPC Section 4.8 • PIL Section 2 • PIL Section 4 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 20140114 See Section II.C of this summary for an overview of the postauthorization development plan

Important identified risk: Hypercalcemia Several Months After the Last Dose in Patients With Giant Cell Tumor of Bone and in Patients With Growing Skeletons	
Evidence for linking the risk to the medicine	This risk was identified in phase 2 clinical trials of adolescent and adult patients with giant cell tumor of bone (GCTB), and in postmarketing reports of pediatric patients using denosumab for unauthorized indications.
Risk factors and risk groups	Patients with GCTB and young patients with growing skeletons following discontinuation of XGEVA. In general, the most common cause of hypercalcemia in humans is hyperparathyroidism, particularly among women and individuals aged 65 years or older (Minisola et al, *BMJ*, 2015;350:h2723). Hyperthyroidism and rhabdomyolysis associated with renal failure also increase the risk of hypercalcemia, as does the ingestion of large of amounts of calcium through dairy products or more recently liberal use of calcium supplements (Machado et al, *J Clin Med*, 2015; 4:414-424; Minisola et al, *BMJ*, 2015;350:h2723).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 4.8 • PIL Section 2 • PIL Section 4 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 20140114 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	The risk of cardiovascular events is a regulatory concern based on the epidemiological association between osteoprotegerin (OPG) levels and cardiovascular disease in man. Clinical data have not substantiated a cause-and-effect between OPG and atherosclerotic processes nor between denosumab or inhibition of receptor activator of nuclear factor kappa B-ligand (RANKL) and undesirable cardiovascular outcomes.
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, gender, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes, and concomitant medications, including antipsychotic agents and cyclooxygenase-2 (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	Imbalance is observed in the new primary malignancy (NPM) events between the zoledronic acid and XGEVA treatment groups in the pivotal clinical studies. The results of Study 20170728, a postmarketing retrospective cohort study, showed NPM incidence rates for XGEVA were generally lower than those for zoledronic acid in unadjusted analyses, suggesting no obvious excess risk associated with XGEVA.
Risk factors and risk groups	General factors for increasing risk of new primary malignancy include advancing age, diet, cigarette smoking, excessive ethanol consumption, and numerous environmental toxins. In addition, advanced cancer populations are at increased risk for NPM because of their existing malignancy, possible genetic predisposition, and exposure to chemotherapy and radiation treatment.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 4.8 • SmPC Section 5.1 • PIL Section 4 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 20140114 See Section II.C of this summary for an overview of the postauthorization development plan

Important potential risk: Delay in Diagnosis of Primary Malignancy in Giant Cell Tumor of Bone	
Evidence for linking the risk to the medicine	The risk of delay in diagnosis of primary malignancy in giant cell tumor of bone is a regulatory concern based on difficulties in diagnosing primary malignancy in giant cell tumor of bone (PMGCTB). This safety concern was identified in the clinical trial setting.
Risk factors and risk groups	Patients with GCTB are known to be at risk for PMGCTB.
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 20140114 See Section II.C of this summary for an overview of the postauthorization development plan

Important potential risk: Hypercalcemia Several Months After the Last Dose in Patients Other Than Those With Giant Cell Tumor of Bone or Growing Skeletons	
Evidence for linking the risk to the medicine	Hypercalemia several months after the last dose in patients other than those with GCTB or growing skeletons is a theoretical concern based on the identified risk in other specific populations, GCTB, and pediatric populations.
Risk factors and risk groups	Patients other than those with GCTB or growing skeletons following cessation of XGEVA.
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None

Missing Information: Patients With Previous Intravenous Treatment With Bisphosphonate Treatment	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.5 • SmPC Section 5.1 • PIL Section 2 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 20101102 See Section II.C of this summary for an overview of the postauthorization development plan

Missing Information: Safety with long term treatment and with long term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumor of bone	
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None

Missing Information: Off label use in patients with giant cell tumor of bone that is resectable where resection is unlikely to result in severe morbidity	
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None

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 XGEVA®.

II.C.2 Other Studies in Postauthorization Development Plan

Study Short Name	Purpose of the Study
Study 20101102: Osteonecrosis of the jaw (ONJ) case registry	Primary objectives: • To estimate the rate and describe the time course of resolution of ONJ. Safety concerns addressed: • Osteonecrosis of the jaw • Patients with prior intravenous bisphosphonate treatment
Study 20140114: Long-term safety follow-up of subjects with giant cell tumor of bone treated with denosumab in Study 20062004	Primary objectives: • Evaluate adverse events of interest in subjects with GCTB treated with denosumab in Study 20062004. Secondary objectives: • Evaluate treatment-emergent adverse events for subjects who are receiving denosumab; • Evaluate serious adverse events for all subjects; • Summarize the rate of disease progression or recurrence of GCTB for all subjects; and • Summarize the use of GCTB interventions for all subjects. Safety concerns addressed: • Osteonecrosis of the jaw • Atypical femoral fracture • Delay in diagnosis of primary malignancy in giant cell tumor of bone • Malignancy • Hypercalcemia several months after the last dose in patients with giant cell tumor of bone and in patients with growing skeletons

PART VII: ANNEXES

Annex 4. Specific Adverse Drug Reaction Follow-up Forms

Table of Contents

AMGEN®

DENOSUMAB Core Questionnaire Osteonecrosis of the Jaw

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

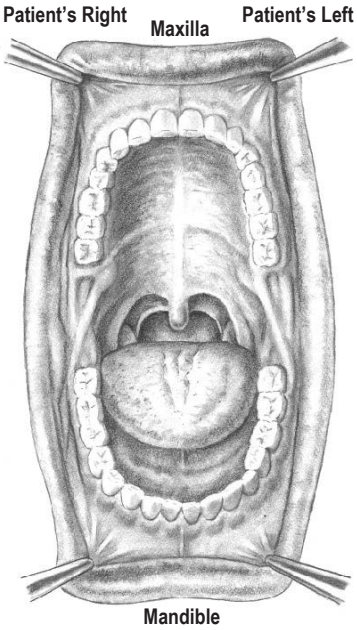
Denosumab first administered (date) _____
Last denosumab dose before event (date) _____
☐ Doses of denosumab were skipped ☐ No ☐ Yes ☐ Unknown
If yes, please specify _____
☐ Doses of denosumab given after event began ☐ No ☐ Yes ☐ Unknown
If yes, date of first dose following start of event _____

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:

Amgen
Office Fax:

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

CONTINUED ON NEXT PAGE

AMGEN®

DENOSUMAB Core Questionnaire Osteonecrosis of the Jaw (continued)

AER #

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:

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

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 #

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

REPORTER

Name:

Address:

City:

Country:

State/ Province:

Postal Code:

Email:

Phone: (include country code)

Signature _____

Title _____ **Date** _____

Amgen
Office Fax:

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

Approved key messages of the additional risk minimization measures

Physician educational material:

- **Patient card**
- **Patient reminder card:**

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

The patient reminder card is intended to remind patients about important safety information that they need to be aware of before and during treatment with denosumab (XGEVA®) injections for cancer-related conditions, including:

- to tell their doctor/nurse if they have any problems with their mouth or teeth before starting treatment;
- to maintain good oral hygiene and receive routine dental check-ups during treatment;
- to inform their doctor and tell their dentist that they are being treated with denosumab (XGEVA®) if they are under dental treatment or will undergo dental surgery;
- to contact their doctor and dentist immediately if they experience any problems with their mouth or teeth such as loose teeth, pain or swelling, nonhealing of sores, or discharge.