EU RISK MANAGEMENT PLAN FOR OSQAY® (DENOSUMAB)

RMP version to be assessed as part of this application

RMP version number:	1.0
Data lock point for this RMP:	01 Jul 2025
Date of final sign-off:	07 Jul 2025
Rationale for submitting an updated RMP:	Not applicable for initial marketing authorisation application submission
Summary of significant changes in this RMP	Not applicable (initial submission)

Other RMP versions under evaluation

RMP version number:	Not applicable
Submitted on:	Not applicable
Procedure number:	Not applicable

Details of the currently approved RMP

Version number:	Not applicable
Approved with procedure:	Not applicable
Date of approval (opinion date):	Not applicable

QPPV name: Birger Fels

[redacted]

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LIST OF ABBREVIATIONS

ADT	androgen deprivation therapy
ADR	adverse drug reaction
AE	adverse experience
AESI	adverse events of special interest
AFF	atypical femoral fracture
AIDS	acquired immune deficiency syndrome
ATC	Anatomical Therapeutic Chemical (classification system)
AUC	area under the concentration-time curve
BCVA	best corrected visual acuity
BMD	bone mineral density
CHO	Chinese hamster ovary
COPD	chronic obstructive pulmonary disease
DLP	data lock point
DXA	dual-energy X-ray absorptiometry
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FDA	US Food and Drug Administration
GC	glucocorticoid
HALT	hormone ablation therapy
HIV	human immunodeficiency virus
HR	hazzard ratio
IBD	inflammatory bowel disease
ICH	International Conference on Harmonization
IgE	immunoglobulin E
IgG	immunoglobulin G
IgG2	immunoglobulin G subclass 2
INN	International Nonproprietary Name
LHRH	luteinizing hormone releasing hormone
LOCS III	Lens Opacities Classification System III

MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MOP	male osteoporosis
NO	nuclear opalescence
OI	osteogenesis imperfecta
ONJ	osteonecrosis of the jaw
OPG	osteoprotegrin
OPG-Fc	osteoprotegrin bound to Fc
P	posterior subcapsular
PI	Product Information
PIP	Paediatric Investigation Plan
PL	package leaflet
PMO	Post-menopausal osteoporosis
PMR	polymyalgia rheumatica
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PTH	parathyroid hormone
PTHrP	parathyroid hormone-related protein
Q3M	once every 3 months
Q6M	once every 6 months
QD	once a day
QPPV	Qualified Person for Pharmacovigilance
RA	rheumatoid arthritis
RANK	receptor activator of nuclear factor kappa B
RANKL	receptor activator of nuclear factor kappa B ligand
RMP	Risk Management Plan
SC	subcutaneous(ly)
SmPC	Summary of Product Characteristics
SOC	System Organ Class (MedDRA)
WHO	World Health Organization

PART I. PRODUCT(S) OVERVIEW

Table Part I.1 Product Overview

Active substance(s) **(INN or common name)**	Denosumab
Pharmacotherapeutic group(s) (ATC Code)	Other drugs affecting bone structure and mineralization (M05BX04)
Marketing Authorisation Applicant	Theramex Ireland Ltd
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Osqay®
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** - Denosumab is a fully human monoclonal antibody of the immunoglobulin G (IgG) 2 subclass.
	Summary of mode of action: - Denosumab binds to and neutralises the activity of human receptor activator of nuclear factor kappa-B (RANK) ligand (RANKL), thereby reducing osteoclast-mediated bone resorption.
	Important information about its composition: - Denosumab is a full-length human monoclonal antibody derived from Xeno-mouse technology™ and is produced in Chinese hamster ovary (CHO) cell lines.
Hyperlink to the Product Information	The proposed product information (PI) is provided in Module 1.3.1.
Indication(s) in the EEA	**Current:** - Treatment of osteoporosis in post-menopausal women and in men at increased risk of fractures. - Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. - Treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture.

	Proposed (if applicable): - Not applicable.
Dosage in the EEA	**Current:** - The recommended dose of Osqay is 60mg administered as a single subcutaneous (SC) injection every 6 months into the thigh, abdomen, or upper arm. Patients must be adequately supplemented with calcium and vitamin D.
	Proposed (if applicable): - Not applicable.
Pharmaceutical form(s) and strengths	**Current (if applicable):** - Osqay is supplied as a sterile, preservative-free solution intended for SC use (solution for injection). Osqay is provided in prefilled syringes at a concentration of 60mg/mL, filled to a targeted deliverable volume of 1.0mL.
	Proposed (if applicable): - Not applicable.
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II. SAFETY SPECIFICATION

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

Not applicable.

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

As Osqay is a biosimilar, no nonclinical program was performed by Theramex. The data included in this section refers to that collected during the nonclinical program conducted by Amgen.

Table SII.1: Summary of Key Safety Findings from Nonclinical Studies and Relevance to Human Usage

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

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

PART II: Module SIII - Clinical Trial Exposure

As Osqay is a biosimilar, a limited clinical development program was performed by Theramex. The data included in this section refers to that collected during the clinical program conducted by Amgen.

Table SIII.1: Total Subject Exposure to Denosumab (Prolia and XGEVA) in Clinical Trials by Product, Indication and Duration - Safety Analysis Set

Exposure to denosumab by duration											
Product indication	≥ 1 year n (subj-yrs	≥ 2 year n (subj-yrs	≥ 3 year n (subj-yrs	≥ 4 year n (subj-yrs	≥ 5 year n (subj-yrs	≥ 6 year n (subj-yrs	≥ 7 year n (subj-yrs	≥ 8 year n (subj-yrs	≥ 9 year n (subj-yrs	≥ 10 year n (subj-yrs	Total n (subj-yrs)
Phase 1 studies	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1439 (450.7)
Prolia											
- PMO	7519 (38315.3)	5624 (35644.1)	4628 (32994.4)	4003 (30929.7)	3587 (29022.4)	3274 (27327.5)	2339 (20920.0)	1633 (15877.0)	1388 (13826.2)	515 (5173.0)	9640 (40184.5)
- MOP	151 (258.2)	27 (54.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	236 (337.9)
- HALT	2957 (9634.3)	2159 (8436.1)	1472 (6702.1)	851 (4587.7)	491 (2921.3)	213 (1414.8)	42 (311.8)	0 (0.0)	0 (0.0)	0 (0.0)	3384 (9966.4)
- RA	49.0 (50.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	144 (140.7)
- GIOP	366 (833.1)	289 (715.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	416 (866.9)
- OI	149 (489.9)	123 (447.7)	96 (376.3)	32 (150.0)	8 (43.6)	2 (12.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	153 (492.4)
Prolia total	11191 (49581.6)	8222 (45297.6)	6196 (40072.8)	4886 (35667.3)	4086 (31987.4)	3489 (28754.6)	2381 (21231.7)	1633 (15877.0)	1388 (13826.2)	515 (5173.0))	13973 (51988.8)
XGEVA total	5723 (18336.3)	3771 (15361.7)	2705 (12774.9)	2046 (10487.2)	523 (3267.5)	168 (1396.4)	96 (932.8)	66 (707.2)	52 (588.0)	42 (493.1)	8768 (19813.1)

Grand total – All studies	**16914 (67917.9)**	**11993 (60659.3)**	**8901 (52847.7)**	**6932 (46154.5)**	**4609 (35254.9)**	**3657 (30151.0)**	**2477 (22164.5)**	**1699 (16584.2)**	**1440 (14414.2)**	**557 (5666.1)**	**24180 (72252.5)**

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

Note: Data from ongoing and completed studies as of 26 Sept 2022. Ongoing Prolia study included 20140444. Ongoing XGEVA study included 20140114. Only Study 20140444 was blinded at time of reporting. Denosumab exposure for ongoing blinded Study 20140444 is based on the number of subjects dosed and the randomization ratio as specified in the protocol. Safety analysis set includes subjects who received at least 1 dose of investigational product.
- For ongoing Prolia studies, subject-years of exposure=(the last exposure date - first non-missing dose date+ 1)/365.25, where last exposure date is the min (date of last non-missing dose+ 180 days - 1), end of study date, data lock point date).
- For completed Prolia studies, subject-years of exposure at the subject level was calculated from the first dose date to the (date of last non-missing dose+ 180 days).
- For ongoing XGEVA studies, subject-years of exposure= (the last exposure date - first non-missing dose date+ 1) / 365.25, where last exposure date is the min ((date of last non-missing dose+ 28 days - 1), end of study date, data lock point date).
- For completed XGEVA studies, subject-years of exposure at the subject level was calculated from the first dose date to the (date of last non-missing dose+ 28 days).
- For subjects who switched treatment across study periods, subject-years of exposure is calculated in the periods in which the study treatment is received.

Modified from program: /userdata/statlamg162/meta/poo/_studies/analysis/rmp2022/tables/t-exposure-prolia-dur.sas Output: t14-05-001-001-exposure-prolia-dur.rtf (Date Generated: 27Nov2022:23:16) Source Data: d202209.dsur_exp.

Table SIII.2: Total Subject Exposure to Denosumab (Prolia and XGEVA) 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 year n (subj-yrs)	≥ 85 years n (subj-yrs)
Male							
Phase 1 studies	0 (0.0)	0 (0.0)	0 (0.0)	521 (147.8)	32 (12.3)	16 (5.5)	5 (1.5)
Prolia							
- PMO	NA	NA	NA	NA	NA	NA	NA
- MOP	0 (0.0)	0 (0.0)	0 (0.0)	105 (150.2)	92 (133.6)	39 (54.1)	0 (0.0)

- HALT	0 (0.0)	0 (0.0)	0 (0.0)	138 (256.3)	546 (1202.0)	550 (1281.5)	67 (165.9)
- RA	0 (0.0)	0 (0.0)	0 (0.0)	36 (35.5)	9 (9.2)	0 (0.0)	0 (0.0)
- GIOP	0 (0.0)	3 (4.4)	10 (18.9)	58 (118.6)	41 (84.0)	18 (36.7)	1 (2.6)
- OI	17 (49.9)	26 (86.6)	37 (127.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Prolia total	17 (49.9)	29 (91.2)	47 (145.9)	337 (560.5)	688 (1428.9)	607 (1372.3)	68 (168.5)
XGEVA total	0 (0.0)	0 (0.0)	5 (18.9)	1511 (2730.1)	1171 (1873.5)	816 (1234.1)	128 (204.2)
Total male	17 (49.9)	29 (91.2)	52 (164.9)	2369 (3438.4)	1891 (3314.6)	1439 (2611.9)	201 (374.1)
Female							
Phase 1 studies	0 (0.0)	0 (0.0)	0 (0.0)	780 (249.0)	68 (28.6)	13 (4.7)	4 (1.3)
Prolia							
- PMO	0 (0.0)	0 (0.0)	0 (0.0)	2035 (5095.7)	5229 (25200.9)	2270 (9618.2)	106 (269.6)
- MOP	NA	NA	NA	NA	NA	NA	NA
- HALT	0 (0.0)	0 (0.0)	0 (0.0)	1101 (3826.3)	793 (2649.3)	184 (568.7)	5 (16.3)
- RA	0 (0.0)	0 (0.0)	0 (0.0)	72 (70.0)	19 (17.9)	7 (7.2)	1 (1.0)
- GIOP	0 (0.0)	0 (0.0)	9 (13.4)	143 (315.2)	82 (172.9)	44 (85.5)	7 (14.8)
- OI	22 (66.4)	26 (79.7)	24 (79.7)	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)
Prolia total	22 (66.4)	26 (79.7)	33 (93.1)	3352 (9310.1)	6123 (28041.0)	2505 (10279.6)	119 (301.7)
XGEVA total	0 (0.0)	0 (0.0)	23 (72.2)	3994 (11308.0)	860 (1941.8)	229 (381.6)	31 (48.7)

Total female	22 (66.4)	26 (79.7)	56 (165.3)	8216 (20867.1)	7051 (30011.4)	2747 (10665.9)	154 (351.7)

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

Note: Data from ongoing and completed studies as of 26 Sept 2022. Ongoing Prolia study included 20140444. Ongoing XGEVA study included 20140114. Only Study 20140444 was blinded at time of reporting. Denosumab exposure for ongoing blinded Study 20140444 is based on the number of subjects dosed and the randomization ratio as specified in the protocol. Safety analysis set includes subjects who received at least 1 dose of investigational product.
- For ongoing Prolia studies, subject-years of exposure=(the last exposure date - first non-missing dose date+ 1) / 365.25, where last exposure date is the min (date of last non-missing dose+ 180 days - 1), end of study date, data lock point date).
- For completed Prolia studies, subject-years of exposure at the subject level was calculated from the first dose date to the (date of last non-missing dose+ 180 days).
- For ongoing XGEVA studies, subject-years of exposure=(the last exposure date - first non-missing dose date+ 1)/365.25, where last exposure date is the min (date of last non-missing dose+ 28 days - 1), end of study date, data lock point date).
- For completed XGEVA studies, subject-years of exposure at the subject level was calculated from the first dose date to the (date of last non-missing dose+ 28 days).
- For subjects who switched treatment across study periods, subject-years of exposure is calculated in the periods in which the study treatment is received.

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

Table SIII.3: Exposure to Denosumab (Prolia) in Clinical Trials by Dose Level and Indication – Safety Analysis Set

	Exposure to denosumab in years			Subject exposure to denosumab		
	<60mg n (mean)	60mg n (mean)	>60mg n (mean)	<60mg n (subj-yrs)	60mg n (subj-yrs)	>60mg n (subj-yrs)
Phase 1	141 (0.5)	496 (0.5)	159 (0.5)	141 (71.0)	496 (246.5)	159 (78.8)
PMO	233 (1.8)	9437 (4.2)	138 (2.1)	233 (418.8)	9437 (39471.2)	138 (294.5)
MOP	0 (0.0)	236 (1.4)	0 (0.0)	0 (0.0)	236 (337.9)	0 (0.0)
HALT	0 (0.0)	3384 (2.9)	0 (0.0)	0 (0.0)	3384 (9966.4)	0 (0.0)
RA	0 (0.0)	71 (1.0)	73 (1.0)	0 (0.0)	71 (70.6)	73 (70.1)
GIOP	22 (1.7)	394 (2.1)	0 (0.0)	22 (36.7)	394 (830.1)	0 (0.0)
OI	153 (3.2)	0 (0.0)	0 (0.0)	153 (492.4)	0 (0.0)	0 (0.0)
Total	**549 (1.9)**	**14018 (3.6)**	**370 (1.2)**	**549 (1018.9)**	**1418 (50922.8)**	**370 (443.4)**

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

Note: Data from ongoing and completed studies as of 26 Sep 2022. Ongoing Prolia study included 20140444. Only Study 20140444 was blinded at time of reporting. Denosumab exposure for ongoing blinded Study 20140444 is based on the number of subjects dosed and the randomization ratio as specified in the protocol. Safety analysis set includes subjects who received at least 1 dose of investigational product.
- For ongoing Prolia studies, subject-years of exposure=(the last exposure date - first non-missing dose date+ 1)/365.25, where last exposure date is the min (date of last non-missing dose+ 180 days - 1), end of study date, data lock point date).
- For completed Prolia studies, subject-years of exposure at the subject level was calculated from the first dose date to the (date of last non-missing dose+ 180 days). For subjects who switched treatment across study periods, subject-years of exposure is calculated in the periods in which the study treatment is received.
Program: /userdatalstatlamg162/metalpoo/_studies/analysis/rrnp2022/tableslt-exposure-prolia-dose.sas
Output: t14-05-001-004-exposure-prolia-dose.rtf (Date Generated: 27 Nov 2022:23:16) Source Data: adam.aslinfo.

Table SIII.4: 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)		
	<120mg n (mean)	120mg n (mean)	>120mg n (mean)	<120mg n (subj-yrs)	120mg n (subj-yrs)	>120mg n (subj-yrs)
Phase 1	65 (0.1)	554 (0.1)	24 (0.1)	65 (5.2)	554 (46.4)	24 (2.8)
CRPC	0 (0.0)	840 (2.1)	0 (0.0)	0 (0.0)	840 (1771.8)	0 (0.0)
BCAT*	0 (0.0)	2241 (3.7)	0 (0.0)	0 (0.0)	2241 (8392.0)	0 (0.0)
GCTB	0 (0.0)	548 (3.7)	0 (0.0)	0 (0.0)	548 (2000.5)	0 (0.0)
HCM	0 (0.0)	33 (0.3)	0 (0.0)	0 (0.0)	33 (10.0)	0 (0.0)
MM	0 (0.0)	95 (0.8)	0 (0.0)	0 (0.0)	95 (72.3)	0 (0.0)
SRE Solid Tumor**	84 (0.4)	3351 (1.4)	163 (0.5)	84 (35.7)	3351 (4638.7)	163 (84.0)
SRE MM	0 (0.0)	1268 (2.1)	0 (0.0)	0 (0.0)	1268 (2706.1)	0 (0.0)
NSCLC	0 (0.0)	145 (0.7)	0 (0.0)	0 (0.0)	145 (101.9)	0 (0.0)
Total	**149 (0.3)**	**9075 (2.2)**	**187 (0.5)**	**149 (40.9)**	**9075 (19739.7)**	**187 (86.8)**

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

Note: Data from ongoing and completed XGEVA studies as of 26 Sep 2022. Ongoing XGEVA study included 20140114. Safety analysis set includes subjects who received at least 1 dose of investigational product.
*Study 20060359 (BCAT) dosed XGEVA Q3 or Q4 weeks for 6 months then Q3 months for up to 4.5 years.
**Study 20050244 is included in SRE Solid Tumor Category, although the study includes a small portion of MM patients.
- For ongoing XGEVA studies, subject-years of exposure=(the last exposure date - first non-missing dose date+ 1)/365.25, where last exposure date is the min (date of last non-missing dose+ 28 days - 1), end of study date, data lock point date).
- For completed XGEVA studies, subject-years of exposure at the subject level was calculated from the first dose date to the (date of last non-missing dose+ 28 days).
- For subjects who switched treatment across study periods, subject-years of exposure is calculated in the periods in which the study treatment is received.

Program: /userdatalstatlamg162/metalpoo/_studieslanalysislrrnp2022/tableslt-exposure-xgeva-dose.sas
Output: t14-05-001-008-exposure-xgeva-dose.rtf (Date Generated: 27NOV2022:23:16) Source Data: adam.aslinfo.

Table SIII.5: Total Subject Exposure to Denosumab (Prolia and XGEVA) in Clinical Trials by Product and Race or Ethnic Group - Safety Analysis Set

Study type Product indication	White n (subj-yrs)	Black or African American n (subj-yrs)	Hispanic or Latino n (subj-yrs)	Asian n (subj-yrs)	Other n (subj-yrs)	Missing/Unknown n (subj-yrs)	Total n (subj-yrs)
Phase 1 studies	1129 (375.4)	186 (32.4)	33 (16.4)	67 (20.0)	24 (6.5)	0 (0.0)	1439 (450.7)
Prolia							
- PMO	8721 (37061.3)	79 (332.4)	568 (2400.7)	235 (326.7)	37 (63.4)	0 (0.0)	9640 (40184.5)
- MOP	223 (325.7)	1 (1.0)	9 (8.3)	2 (1.9)	1 (1.0)	0 (0.0)	236 (337.9)
- HALT	3171 (9453.2)	54 (125.1)	120 (323.0)	26 (48.4)	13 (16.7)	0 (0.0)	3384 (9966.4)
- RA	121 (119.6)	4 (3.0)	11 (10.7)	3 (3.0)	5 (4.4)	0 (0.0)	144 (140.7)
- GIOP	365 (761.9)	6 (8.4)	0 (0.0)	17 (36.0)	28 (60.6)	0 (0.0)	416 (866.9)
- OI	135 (433.0)	2 (7.8)	0 (0.0)	4 (13.7)	12 (37.9)	0 (0.0)	153 (492.4)

Prolia total	12736 (48154.6)	146 (477.7)	708 (2742.7)	287 (429.8)	96 (184.0)	0 (0.0)	13973 (51988.8)
XGEVA total	7082 (15778.9)	317 (696.9)	472 (972.2)	758 (2055.9)	137 (304.1)	2 (5.2)	8768 (19813.1)
Grand total – All studies	**20947 (64308.8)**	**649 (1207.0)**	**1213 (3731.3)**	**1112 (2505.7)**	**257 (494.5)**	**2 (5.2)**	**24180 (72252.5)**

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

Note: Data from ongoing and completed studies as of 26 Sept 2022. Ongoing Prolia study included 20140444. Ongoing XGEVA study included 20140114. Only Study 20140444 was blinded at time of reporting. Denosumab exposure for ongoing blinded Study 20140444 is based on the number of subjects dosed and the randomization ratio as specified in the protocol. Safety analysis set includes subjects who received at least 1 dose of investigational product.
- For ongoing Prolia studies, subject-years of exposure=(the last exposure date - first non-missing dose date+ 1) / 365.25, where last exposure date is the min (date of last non-missing dose+ 180 days - 1), end of study date, data lock point date).
- For completed Prolia studies, subject-years of exposure at the subject level was calculated from the first dose date to the (date of last non-missing dose+ 180 days).
- For ongoing XGEVA studies, subject-years of exposure=(the last exposure date - first non-missing dose date+ 1)/365.25, where last exposure date is the min (date of last non-missing dose+ 28 days - 1), end of study date, data lock point date).
- For completed XGEVA studies, subject-years of exposure at the subject level was calculated from the first dose date to the (date of last non-missing dose+ 28 days).
- For subjects who switched treatment across study periods, subject-years of exposure is calculated in the periods in which the study treatment is received.

Modified from program: /userdata/statlamg162/meta/poo/_studies/analysis/rmp2022/tables/t-exposure-prolia-age-sex.sas
Output: t14-05-001-002-exposure-prolia-age-sex.rtf (Date Generated: 27NOV2022:23:16) Source Data: d202209.dsur_exp, r140444.demog_al.

Table SIII.6: Total Subject Exposure to Denosumab (Prolia and XGEVA) in Clinical Trials in Subjects With Renal Impairment – Safety Analysis Set

Product Baseline Calculated Creatinine Clearance*	Exposure to Denosumab in Subjects With Serum Creatinine Collected at Baseline n (subj-yrs)
Phase 1 studies	
- Mild	270 (98.7)
- Moderate	42 (18.7)
- Severe	26 (6.7)
- Kidney failure	22 (6.1)
Total	**360 (130.3)**
Prolia	
- Mild	6802 (26501.2)
- Moderate	3942 (15866.9)
- Severe	84 (273.8)
- Kidney failure	2 (7.1)

Total	**10830 (42648.9)**
XGEVA	
- Mild	2293 (3806.6)
- Moderate	1154 (1681.2)
- Severe	36 (50.2)
- Kidney failure	2 (1.7)
Total	**3485 (5539.7)**
Overall total	
- Mild	9365 (30406.5)
- Moderate	5138 (17566.8)
- Severe	146 (330.7)
- Kidney failure	26 (14.9)
Total	**14675 (48318.9)**

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

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

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

- For ongoing Prolia studies, subject-years of exposure=(the last exposure date - first non-missing dose date + 1)/365.25, where last exposure date is the min (date of last non-missing dose + 180 days - 1), end of study date, data lock point date).
- For completed Prolia studies, subject-years of exposure at the subject level was calculated from the first dose date to the (date of last non-missing dose+ 180 days).
- For ongoing XGEVA studies, subject-years of exposure=(the last exposure date - first non-missing dose date+ 1)/365.25, where last exposure date is the min (date of last non-missing dose+ 28 days - 1), end of study date, data lock point date).
- For completed XGEVA studies, subject-years of exposure at the subject level was calculated from the first dose date to the (date of last non-missing dose+ 28 days).
- For subjects who switched treatment across study periods, subject-years of exposure is calculated in the periods in which the study treatment is received.

Program: /userdata/statlamg162/meta/poo/_studies/analysis/rmp2022/tables/t-exposure-renal.sas.
Output: t14-05-001-009-exposure-renal.rtf (Date Generated: 27NOV2022:23:16) Source Data: adam.aslinfo.

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

As Osqay is a biosimilar, and therefore only underwent a limited clinical program, the data included in this section refers to that collected during the Prolia clinical development program conducted by Amgen.

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

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale (if not included as missing information)
Contraindications			
Hypocalcaemia	Hypocalcaemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy. Patients receiving denosumab must have adequate intake of calcium and vitamin D. This information is provided in the Osqay SmPC.	No	It is a contraindication in the SmPC.
Hypersensitivity to the active substance or to any of the excipients	Patients who are hypersensitive to denosumab, or to any of the excipients listed in Section 6.1 of the Osqay SmPC, should not receive Osqay.	No	It is a contraindication in the SmPC.
Exclusion criteria applying to PMO, HALT, and GIOP studies			
BMD T-score < -4	It was considered unethical to enrol subjects with a T-score < -4.0 in placebo-controlled studies when approved therapies were available, because these subjects would remain untreated for 3 years if randomized to the placebo group.	No	The safety and efficacy of denosumab is not expected to differ in subjects with lower BMD T-scores. In subgroup analyses by baseline lumbar spine and total hip T-score for the range of T-scores enrolled in the large pivotal PMO study (Study 20030216), denosumab was effective in each subgroup. Therefore, no special dosing recommendations

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale (if not included as missing information)
			for patients with BMD T-scores < -4.0 are considered necessary. Furthermore, subjects with BMD T-scores < -4.0 were not excluded from the pivotal study in the GIOP population (Study 20101217) because the study was active-controlled (risedronate).
Other bone diseases	Patients with other bone diseases such as RA, OI, and Paget's disease were excluded from the pivotal osteoporosis studies because other bone diseases could confound the efficacy results.	No	Osqay is not indicated for use in these other patient populations. However, subjects with RA were not excluded from Amgen's Prolia pivotal study in the GIOP population (Study 20101217), because RA is a common indication for GC use.
Exclusion criteria applying to osteoporosis studies only			
Previous bisphosphonate treatment	Subjects with previous bisphosphonate treatment were excluded from pivotal osteoporosis studies in accordance with regulatory guidance to demonstrate fracture benefit in a PMO population. Because bisphosphonates incorporate into bone and long-term use of bisphosphonates is associated with continued effects of the drug after treatment is stopped, it was deemed most appropriate to exclude previous bisphosphonate treatment.	No	In Amgen Study 20050234, a double-blind, alendronate-controlled, study in postmenopausal women with low BMD who had received bisphosphonates for at least 6 months preceding study entry, safety results were similar in the denosumab and alendronate treatment groups. In addition, Studies 20080099, 20080562, and 20110153 evaluated the effects of Prolia and a bisphosphonate

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale (if not included as missing information)
			(risedronate, ibandronate, or zoledronic acid, respectively) in postmenopausal women transitioning from previous bisphosphonate therapy. There were no new safety findings in these studies.
Evidence of distant metastases	Subjects with distant metastases have been evaluated in other clinical studies of denosumab using a different dose and schedule (up to 120mg monthly).	No	An indication in this patient population was not sought for denosumab 60mg. Xgeva (denosumab 120mg) is approved for the prevention of skeletal-related events in adults with bone metastases from solid tumours; thus, safety in this population is well documented.
Exclusion criteria applying to HALT studies only			
Serum creatinine > 2.0mg/dL	Treatment with antiresorptive agents reduces the ability to mobilize calcium from bone; thus, hypocalcaemia could be exacerbated in patients with renal impairment.	No	Amgen Study 20040245 demonstrated that renal impairment does not affect the pharmacokinetics of denosumab; therefore, no dose adjustments are required in patients with impaired renal function. Recommendations for adequate intake of calcium and vitamin D in all patients, and recommendations for monitoring of serum calcium in patients predisposed to hypocalcaemia, have been included in the Osqay SmPC. No other

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale (if not included as missing information)
			special dosing recommendations are considered necessary for subjects with renal impairment.
Exclusion criteria applying to all indications			
Subjects who are pregnant or breastfeeding or planning to become pregnant.	Adequate and well-controlled studies with denosumab have not been conducted in pregnant women due to the potential risk to the fetus. It is not known whether denosumab is excreted into human breast milk.	No	These populations are not included in the intended indications. Risk minimization via product labelling instructing patients to avoid pregnancy and breast feeding is in place. No additional pharmacovigilance activities or additional risk minimization measures are warranted.

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

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

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

SIV.3 Limitations in Respect to Populations Typically Underrepresented in Clinical Trial Development Programs

Table SIV.3.1: Exposure of Special Populations Included or not in Clinical Trial Development Programs

Type of special population	Exposure
- Pregnant women	- Eight pregnancies were reported in the Prolia clinical development program.
- Breast-feeding women	- No cases of breast-feeding were reported in the Prolia clinical development program.

Patients with relevant comorbidities	
- Patients with hepatic impairment	- Not included in the Prolia clinical development program.
- Patients with renal impairment	- Subjects with renal impairment were not specifically excluded from the Prolia clinical studies. A total of 6802 subjects (26,501.2 subject-years), 3942 subjects (15,866.9 subject-years), 84 subjects (273.8 subject-years), and 2 subjects (7.1 subject-years) with mild, moderate, or severe renal impairment, or kidney failure, respectively, were exposed to denosumab in the Prolia clinical development program.
- Patients with cardiovascular impairment	- In a large pivotal PMO study (Study 20030216), a sub-study was conducted in 2363 subjects with high cardiovascular risk.
- Immunocompromised patients	- No specific exclusions, except for HIV-positive patients.
- Patients with a disease severity different from the inclusion criteria in the Prolia clinical development program	- Not included in the Prolia clinical development program.
Populations with relevant different ethnic origins	- A total of 12,736 subjects (48,154.6 subject-years), 146 subjects (477.7 subject-years), 708 subjects (2742.7 subject-years), and 287 subjects (429.8 subject-years) of white, black or African American, Hispanic or Latino, or Asian race/ethnicity, respectively, were exposed to denosumab in the Prolia clinical development program. In pivotal studies, 451 of the 4910 subjects who received denosumab belonged to an ethnic or racial minority (PMO: 321/4050; HALT 130/860).
- Subpopulations carrying relevant genetic polymorphisms	- Not included in the Prolia clinical development program.
Other special populations	
- Paediatric patients	

- Geriatric patients	Males: A total of 17 subjects (49.9 subject-years), 29 subjects (91.2 subject-years), and 47 subjects (145.9 subject-years) aged 2 to 6 years, 7 to 10 years, and 11 to 17 years, respectively, were exposed to denosumab in the Prolia clinical development program. Females: A total of 22 subjects (66.4 subject-years), 26 subjects (79.7 subject-years), and 33 subjects (93.1 subject-years) aged 2 to 6 years, 7 to 10 years, and 11 to 17 years, respectively, were exposed to denosumab in the Prolia clinical development program. This population was not underrepresented in the Prolia clinical development program (see table SIII.2). Males: A total of 688 subjects (1428.9 subject-years), 607 subjects (1372.3 subject-years), and 68 subjects (168.5 subject-years) aged 65 to 74 years, 75 to 84 years, and ≥85 years, respectively, were exposed to denosumab in the Prolia clinical development program. Females: A total of 6123 subjects (28,041.0 subject-years), 2505 subjects (10,279.6 subject-years), and 119 subjects (301.7 subject-years) aged 65 to 74 years, 75 to 84 years, and ≥85 years, respectively, were exposed to denosumab in the Prolia clinical development program.
- Patients with a BMD T-score < -4.0	Subjects with a BMD T-score < -4.0 were not explicitly excluded from Prolia clinical studies, except in Study 20030216.

BMD=bone mineral density; HALT=hormone ablation therapy; HIV=human immunodeficiency virus; PMO=postmenopausal osteoporosis.

PART II: Module SV – Post-Authorization Experience

SV.1 Post-Authorisation Exposure

SV.1.2 Exposure

At the time of the initial RMP, Osqay® is not yet commercialized. However, to provide the reader with a sense of denosumab exposure in the post-markeing setting, the exposure presented in the Prolia RMP (Version 31.0; 11 Jan 2023]) is provided.

The estimated cumulative number of patient-years of exposure and patients exposed to Prolia through commercial distribution are shown in Table SV 1.2.1 and Table SV 1.2.2, respectively. Cumulatively, through 26 Sep 2022, the total worldwide postmarketing patient exposure, which includes both Amgen and business partner territories, was 33,161,236 patient-years.

Table SV 1.2.1 Estimated Number of Patient-years of Exposure to Denosumab (Prolia, CORORA) in the Postmarketing Setting, by Region and Demographic Characteristics

Demographic Characteristic[a]	Cumulative[b] Number of Patient-years of Exposure					
	AU	CA	EUR	US	Other[c]	Total
Overall	2,903,246	1,553,291	11,686,873	7,376,108	5,526,297	29,045,814
Sex						
- Female	2,573,934	1,372,675	10,284,213	6,515,102	4,951,634	25,697,560
- Male	329,312	180,617	1,402,659	861,004	574,663	3,348,254
Age						
- 18-34	4830	2724	21,878	13,040	7540	50,011
- 35-49	76,890	43,215	345,651	206,769	121,886	794,410
- 50-64	800,534	446,503	3,539,160	2,133,928	1,309,311	8,229,435
- 65-74	895,101	464,319	3,349,597	2,193,999	1,875,592	8,778,609
- ≥75	1,125,892	596,531	4,430,587	2,828,372	2,211,968	11,193,349
Sex/age						
- Female						
- 18-34	4152	2349	18,932	11,251	6403	43,089
- 35-49	69,256	38,984	312,367	186,566	109,078	716,249
- 50-64	726,728	405,117	3,209,029	1,935,977	1,191,195	7,468,044
- 65-74	804,956	415,375	2,974,309	1,961,050	1,712,410	7,868,100
- ≥75	968,843	510,851	3,769,577	2,420,261	1,932,548	9,602,078
- Male						
- 18-34	676	375	2945	1789	1138	6924
- 35-49	7636	4231	33,284	20,204	12,807	78,161
- 50-64	73,709	41,340	329,850	197,739	117,856	760,494
- 65-74	90,243	48,989	375,569	233,162	163,442	911,404
- ≥75	157,049	85,681	661,010	408,111	279,421	1,591,271

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

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

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

easily testable.
[b] Cumulatively through 26 Sep 2022
[c] Does not include Japan

Table SV 1.2.2 Estimated Number of Patients Exposued to Denosumab (Prolia, CORORA) in the Postmarketing Setting, by Region and Demographic Characteristics

Demographic Characteristic[a]	Cumulative[b] Number of Patients Exposed					
	AU	CA	EUR	US	Other[c]	Total
Overall	2,087,514	1,160,033	9,097,040	5,585,318	3,626,854	21,556,759
Sex						
- Female	1,833,760	1,016,279	7,944,625	4,890,552	3,214,937	18,900,154
- Male	253,755	143,753	1,152,415	694,766	411,916	2,656,603
Age						
- 18-34	4009	2315	18,948	11,229	6050	42,550
- 35-49	63,246	36,432	297,474	176,644	96,301	670,098
- 50-64	645,363	369,900	3,003,940	1,791,783	1,002,222	6,813,210
- 65-74	587,738	317,581	2,407,859	1,520,438	1,116,464	5,950,080
- ≥75	787,157	433,806	3,368,820	2,085,223	1,405,816	8,080,821
Sex/age						
- Female						
- 18-34	3475	2009	16,481	9751	5202	36,917
- 35-49	57,195	32,978	269,561	159,929	86,746	606,409
- 50-64	585,020	335,190	2,720,988	1,623,540	909,796	6,174,534
- 65-74	520,186	279,600	2,105,971	1,337,148	1,003,767	5,246,672
- ≥75	667,886	366,502	2,831,625	1,760,184	1,209,426	6,835,624
- Male						
- 18-34	536	305	2467	1478	846	5631
- 35-49	6052	3453	27,914	16,715	9556	63,689
- 50-64	60,299	34,688	282,820	168,144	92,307	638,259
- 65-74	67,597	38,002	302,019	183,389	112,819	703,826
- ≥75	119,271	67305	537,195	325,040	196,390	1,245,199

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

Note: Numbers may not add to the total due to rounding.
[a] Age and sex breakdowns are based on patient characteristics in MarketScan and Optum, US health insurance claims databases. Applying these distributions to regions outside the United States requires strong assumptions that are not easily testable.
[b] Cumulatively through 26 Sep 2022
[c] Does not include Japan[c] Does not include Japan

SV.1.2.1 Postauthorization Use From Business Partners

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

PART II: Module SVI – Additional EU Requirements for the Safety Specification

SVI.1 Potential for Misuse for Illegal Purposes

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

PART II: Module SVII – Identified and Potential Risks

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

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

Not applicable, since the summary of safety concerns is in line with the originator product (Prolia).

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

The list of safety concerns is as per GVP and therefore in line with the safety concerns of the originator product (Prolia).

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

Not applicable (this is an initial submission).

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 SVII.3.1.1 Important Identified Risk: Hypocalcaemia

Potential mechanisms	Denosumab inhibits osteoclast-mediated bone resorption, thereby decreasing the release of calcium from bone into the bloodstream.
Evidence source(s) and strength of evidence	This risk was identified in the phase 3, randomized, double-blind, placebo- or active-controlled studies for Prolia.
Frequency	In the pooled pivotal studies for PMO and HALT, subject incidence of hypocalcemia adverse events was <0.1% in denosumab-treated subjects and 0.1% in placebo-treated subjects. The incidence of hypocalcemia adverse events was lower in denosumab-treated subjects than in placebo-treated subjects; thus, 95% CIs were not calculated. In the 24-month final analysis of the GIOP study, subject incidence of hypocalcemia adverse events was 0.3% in the denosumab group; there were no adverse events of hypocalcemia in the risedronate group; thus, 95% CIs were not calculated.
Severity	While most hypocalcemia events are mild to moderate in severity; severe events have occurred.

Reversibility	Hypocalcemia is reversible when treated with oral calcium and vitamin D supplementation. In severe cases, IV calcium supplementation may be required.
Long-term outcomes	No long-term complications are anticipated for properly treated hypocalcaemia.
Impact on quality of life	For severe symptomatic hypocalcaemia, patients may be hospitalized for treatment. Generally, patients recover when their hypocalcaemia is treated.
Risk factors and risk groups	Risk factors include severe renal impairment and hyperphosphatemia. Other risks factors may include a history of hypoparathyroidism, PTH resistance, vitamin D deficiency or resistance, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, severe renal impairment (CrCL <30mL/min), dialysis, and some medications (Finkelstein, 2001).
Preventability	Pre-existing hypocalcemia should be corrected by adequate intake of calcium and vitamin D before initiating therapy, and supplementation with calcium and vitamin D is important during therapy in all patients receiving denosumab. Clinical monitoring of calcium levels is recommended during treatment, especially in those with renal impairment.
Impact on the risk-benefit balance of the product	The risk of hypocalcemia has been considered in the product benefit-risk assessment. In light of the product labeling addressing this risk, the overall benefit-risk balance is considered to be positive.
Public health impact	Significant public health impact is not expected as this risk is preventable and treatable with the appropriate risk mitigating measures communicated clearly in the SmPC.

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

Table SVII.3.1.2 Important Identified Risk: Skin Infection Leading to Hospitalization

Potential mechanisms	Keratinocytes can express RANKL and blocking RANKL in mice decreased the number of regulatory T-cells in skin, leading to an increased inflammatory response (Loser et al, 2006; Yamaguchi and Sakaguchi, 2006).
Evidence source(s) and strength of evidence	This risk was identified in the phase 3, randomized, double-blind, placebo- or active-controlled studies for Prolia.
Frequency	In pooled PMO/HALT pivotal studies, subject incidence of skin infection was 1.4% with denosumab and 1.3% with placebo; the HR was 1.09 (95% CI: 0.78, 1.53). Subject incidence of serious adverse events of skin infection was 0.4% with denosumab and 0.2% with placebo (HR [95% CI] =2.55 [1.13, 5.76]). In the 24-month final analysis of the GIOP study, subject incidence of adverse events of skin infection was 1.8% with denosumab and 0.5% with risedronate; the HR was

	3.62 (95% CI =0.75, 17.42). Subject incidence of serious adverse events of skin infection was 0.5% in both the denosumab and risedronate groups (HR [95% CI] =1.03 [0.15, 7.34]).
Severity	Serious adverse events of skin infection were mostly severe in intensity.
Reversibility	These events typically resolved with administration of antibiotics.
Long-term outcomes	No long-term complications are anticipated for properly treated patients who are hospitalized due to skin infections.
Impact on quality of life	Requires a hospital stay; patients generally recover with antibiotic treatment.
Risk factors and risk groups	Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, HIV/AIDS, immunosuppressant drugs (e.g., corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition. Risk factors for skin infection in older patients include skin wounds, peripheral vascular disease, eczema/dermatitis, and venous stasis disorders.
Preventability	No preventative measures are known.
Impact on the risk-benefit balance of the product	The risk of skin infection leading to hospitalisation has been considered in the product risk-benefit assessment. In light of the product labelling addressing this risk, the overall benefit-risk balance is considered to be positive.
Public health impact	Since the frequency of skin infection leading to hospitalisation is relatively low, absolute difference between denosumab and placebo groups is relatively small, and the adverse events can be effectively treated by antibiotics, the negative impact to public health is relatively small.

AIDS=acquired immune deficiency syndrome; CI=confidence interval; GIOP=glucocorticoid-induced osteoporosis; HALT=hormone ablation therapy; HIV=human immunodeficiency virus; HR=hazzard ratio; PMO=postmenopausal osteoporosis; RANKL=receptor activator of nuclear kappa-BSmPC=summary of product characteristics.

Table SVII.3.1.3 Important Identified Risk: Osteonecrosis of the Jaw

Potential mechanisms	Osteonecrosis of the jaw (ONJ) appears to be multifactorial and multiple hypotheses have been postulated and have included factors such as inhibition of bone remodeling, infection and inflammation, inhibition of angiogenesis, soft tissue toxicity, altered immunity and genetic predisposition. As yet, evidence supporting these hypotheses has been variable and little is understood in how these multiple pathways might interact (Fassio et al, 2017; Aghaloo et al, 2015).
Evidence source(s) and strength of evidence	This risk was identified in open-label long-term extensions to phase 3, randomized, double-blind, placebo-controlled studies for Prolia.

Frequency	No cases of ONJ have been reported in placebo-controlled studies (although cases were reported in open-label extensions to the pivotal PMO study and a HALT study); thus, 95% CIs were not calculated. No cases of ONJ were reported in the GIOP study. Overall, across the Amgen-sponsored clinical development program for Prolia, positively adjudicated ONJ cases have been reported rarely (18 ONJ cases in 23,552 subjects, 0.076%) in subjects cumulatively exposed to denosumab (60mg) clinical studies.
Severity	Most events leading to adjudication as ONJ were assessed as moderate in severity. Mild and severe events were also reported.
Reversibility	In general, ONJ events are clinically reversible with supportive care, antibiotics; however, surgical treatment may be required.
Long-term outcomes	No data on long-term outcomes are available.
Impact on quality of life	Discomfort associated with ONJ lesions and/or with more extensive treatments may impact patient wellbeing via decreased oral intake (e.g., decreased hydration and decreased nutritional intake).
Risk factors and risk groups	Risk factors include duration of exposure to denosumab, prior bisphosphonate use (particularly for extended periods of time), older age, periodontal disease, dentoalveolar surgery, trauma from poorly fitting dentures, malignancy, chemotherapy, corticosteroids, smoking, systemic or regional infection, immune-compromised state predisposing to increased risk of infection, hypercoagulable state secondary to underlying malignancy, and vascular insufficiency due to thrombosis (Mehrotra and Ruggiero, 2006; Ruggiero et al, 2006).
Preventability	A dental examination with appropriate preventive dentistry is recommended prior to treatment, 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 Osqay should receive care by a dentist or an oral surgeon. In patients who develop ONJ during treatment with Osqay, a temporary interruption of treatment should be considered based on individual risk/benefit assessment until the condition resolves.
Impact on the risk-benefit balance of the product	The risk of ONJ has been considered in the product benefit-risk assessment. In light of the product labeling, the overall benefit-risk balance is considered to be positive.
Public health impact	Significant public health impact is not expected with Osqay, as the event is rare and the actions taken to minimize the likelihood of developing ONJ are described in the prescribing information.

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

Table SVII.3.1.4 Important Identified Risk: Hypersensitivity Reactions

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

CI=confidence interval; GIOP=glucocorticoid-induced osteoporosis; HALT=hormone ablation therapy; HR=hazzard ratio; IgE=immunoglobulin E; PMO=postmenopausal osteoporosis; SmPC=summary of product characteristics.

Table SVII.3.1.5 Important Identified Risk: Atypical Femoral Fractures

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

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 has been considered in the product benefit-risk assessment. In light of the product labeling addressing this risk, the overall benefit-risk balance is considered to be positive.
Public health impact	Based on the infrequency of AFF in patients treated with denosumab, no significant public health impact is expected.

AFF=atypical femoral fracture; CI=confidence interval; GIOP=glucocorticoid-induced osteoporosis; PPI=proton pump inhibitor; RA=rheumatoid arthritis.

Table SVII.3.1.6 Important Identified Risk: Hypercalcemia in Pediatric Patients Receiving Denosumab and After Treatment Discontinuation

Potential mechanisms	The exact mechanism of hypercalcemia occurring in paediatric patients, both during the dosing interval and following discontinuation, is not certain but may be a consequence of the following, alone, or in combination: - Hypercalcemia may result from rapid resorption of retained primary spongiosa in a skeleton with active endochondral ossification. The rate of endochondral ossification and duration of exposure to denosumab would determine the amount of accumulated primary spongiosa that could influence the magnitude of resorptive response (mechanostat-driven) and release of calcium from resorbing bone matrix via an autocrine/paracrine mechanism. - The magnitude of the resorptive response following treatment and withdrawal in the immature skeleton could be dictated by the normal high rate of bone turnover in individuals with growing skeletons. - The response of the osteoclast lineage to loss of inhibition of osteoclastogenesis may be intrinsically more robust in individuals with growing skeletons. The increased skeletal metabolism related to bone modeling and growth in children is therefore likely to impact the frequency of hypercalcemia occurring both between the dosing interval and following discontinuation.
Evidence source(s) and strength of evidence	Data used to evaluate this safety concern were derived from Prolia clinical trials in pediatric subjects with OI, XGEVA clinical studies, and postmarketing adverse event reporting involving pediatric patients receiving denosumab at unapproved doses and/or unapproved indications for use.
Frequency	In completed pediatric OI Study 20130173, during the Q6M dosing regimen, hypercalcemia (Amgen Medical Dictionary for Regulatory Activities [MedDRA] Query [Narrow Search; AMQN]) was reported for 29 subjects (19.0%). All these events were nonserious. During the Q3M dosing regimen, and following denosumab discontinuation, hypercalcemia (AMQN) was reported for 22 subjects (36.7%). Serious adverse events of hypercalcemia were reported for 8 subjects (13.3%).

Severity	Most subjects in the pediatric OI Study 20130173 who received the Q3M dosing regimen and who had hypercalcemia experienced mild events. Grade ≥3 hypercalcemia was reported for 10 subjects (16.7%). Grade 4 (life-threatening) hypercalcemia was reported for 4 subjects (6.7%).
Reversibility	Hypercalcemia is reversible when treated. In severe cases, use of rescue medications may be required.
Long-term outcomes	No long-term adverse effects are anticipated for properly treated hypercalcemia.
Impact on quality of life	Pediatric patients may present with severe hypercalcemia requiring hospitalization. Generally, patients recover when the hypercalcemia is treated.
Risk factors and risk groups	Pediatric patients with growing skeletons and high bone turnover disease states (e.g., OI).
Preventability	Osqay is not indicated in pediatric patients (aged <18 years) and should not be used in pediatric patients. If used in a clinical trial setting, such as for pediatric GIOP, monitoring for signs and symptoms and periodic serum calcium is advisable.
Impact on the risk-benefit balance of the product	The benefit-risk profile of Osqay (denosumab) is not favorable in the pediatric patient population.
Public health impact	Significant public health impact is not expected as this risk is preventable with the appropriate risk mitigating measures communicated clearly in the SmPC.

AMQN=Amgen MedDRA Query [narrow search]; GIOP=glucocorticoid-induced osteoporosis; MedDRA=Medical Dictionary for Regulatory Activities; OI=osteogenesis imperfecta; Q3M=once every 3 month dosing; Q6M=once every 6 month dosing; SmPC=summary of product characteristics.

Table SVII.3.1.7 Important Potential Risk: Fracture Healing Complications

Potential mechanisms	Because denosumab directly suppresses bone resorption and (indirectly) bone formation, it has the theoretical potential to delay fracture healing.
Evidence source(s) and strength of evidence	This is a theoretical risk based on the mechanism of action.
Frequency	Of the subjects who had nonvertebral fractures in the large pivotal PMO study, fracture healing complications (delayed healing or nonunion) were reported in 2 of 386 subjects in the denosumab group (0.5%) and 5 of 465 subjects (1.1%) in the placebo group. Of the subjects who had nonvertebral fractures in the pivotal study for HALT-breast cancer, fracture healing complications were reported in 0 of 8 subjects in the denosumab group and 1 of 8 subjects (12.5%) in the placebo group. Because of the low incidence of fracture healing complications, 95% Cls were not calculated. No fracture

	healing complications were reported in the MOP study. No fracture healing complications were reported in the GIOP study.
Severity	This risk has not been substantiated; however, impaired fracture healing could have significant impact on patient wellbeing.
Reversibility	This risk has not been substantiated; however, the effects of denosumab on osteoclasts are fully reversible.
Long-term outcomes	This risk has not been substantiated; however, no long-term impact would be anticipated based on reversibility.
Impact on quality of life	Fracture healing complications can cause short-term or long-term disability. Surgery may be required.
Risk factors and risk groups	General risk factors for fracture healing complications are thought to include older age, diabetes, use of medications such as non-steroidal anti-inflammatory drugs and corticosteroids, smoking, excessive alcohol use, and poor nutrition (Hernandez et al, 2012; Gaston and Simpson, 2007).
Preventability	No preventive measures are known.
Impact on the risk-benefit balance of the product	The potential risk of fracture healing complications has been considered in the overall assessment supporting a positive benefit-risk profile.
Public health impact	No significant impact on public health is anticipated.

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

Table SVII.3.1.8 Important Potential Risk: Infection

Potential mechanisms	RANK ligand is expressed on activated T and B cells and in the lymph nodes and some reports have described immune modulatory effects of RANKL inhibition. However, no clinically relevant effect of denosumab treatment was observed on peripheral blood immune cell subset profiles in studies in healthy elderly men, postmenopausal women, and postmenopausal women with low BMD. No evidence of a treatment effect of denosumab on immunoglobulin production was observed.
Evidence source(s) and strength of evidence	This is considered a potential risk based on theoretical concerns which havenot been substantiated in the extensive clinical study program or in the postmarketing experience.
Frequency	

	Subject lncidence[a] (percent)	Hazard ratio (95% Cl)
Adverse events		
Placebo	50.6	0.98 (0.92, 1.03)
Denosumab	50.1	

Serious adverse events			
Placebo	3.4	1.25 (1.02, 1.53)
Denosumab	4.3	
Serious adverse events not including skin infection		
Placebo	3.3	1.18 (0.95, 1.45)
Denosumab	3.9	
Opportunistic infectionb		
Placebo	0.1%	--
Denosumab	0.1%	

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

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

Severity	The majority of reported events of infection were non serious. Serious adverse events were most commonly reported as severe in intensity.
Reversibility	Infections when treated appropriately are generally reversible.
Long-term outcomes	Infection generally responds to appropriate treatment and as such no long-term effects are anticipated.
Impact on quality of life	For severe infection, patients may be hospitalized for treatment. Generally, patients recover when their infection is treated.
Risk factors and risk groups	Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, HIV/AIDS, immunosuppressant drugs (eg, corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition.
Preventability	No preventive measures are known.
Impact on the risk-benefit balance of the product	The potential risk of infection has been considered in the overall assessment which supports a positive benefit-risk profile in the indicated populations.
Public health impact	No significant public health impact is expected for this unsubstantiated risk as effective treatments are available.

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

Table SVII.3.1.9 Important Potential Risk: Cardiovascular Events

<table>
<tr><td>Potential mechanisms</td><td>Elevated levels of OPG have been associated with coronary artery disease in cross-sectional studies; however, 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.</td></tr>
<tr><td>Evidence source(s) and strength of evidence</td><td>This is a theoretical risk based on epidemiological data demonstrating elevated OPG in patients with cardiovascular disease.</td></tr>
<tr><td>Frequency</td><td>In a pooled analysis of the large pivotal PMO study (20030216) and the pivotal HALT-prostate study, the overall subject incidence of adjudicated-positive serious cardiovascular events was 5.8% with denosumab and 5.6% with placebo (HR [95% Cl]=1.00 [0.85, 1.19]). The subject incidence of positively adjudicated, pre-defined categories of serious cardiovascular events was comparable between the treatment groups in the pooled analysis, as shown below:
<table>
<tr><th>Studies 20030216 and 20040138[a]</th><th>Subject lncidence (percent)</th><th>Hazard ratio (95% Cl)</th></tr>
<tr><td>Acute coronary syndrome</td><td></td><td></td></tr>
<tr><td>Placebo</td><td>1.4</td><td>0.96 (0.68, 1.35)</td></tr>
<tr><td>Denosumab</td><td>1.4</td><td></td></tr>
<tr><td>Congestive heart failure</td><td></td><td></td></tr>
<tr><td>Placebo</td><td>0.7</td><td>1.03 (0.64, 1.65)</td></tr>
<tr><td>Denosumab</td><td>0.8</td><td></td></tr>
<tr><td>Stroke/transient ischaemic attack</td><td></td><td></td></tr>
<tr><td>Placebo</td><td>1.5</td><td>1.06 (0.77, 1.46)</td></tr>
<tr><td>Denosumab</td><td>1.7</td><td></td></tr>
<tr><td>Arrhythmia</td><td></td><td></td></tr>
<tr><td>Placebo</td><td>1.3</td><td>1.15 (0.82,1.63)</td></tr>
<tr><td>Denosumab</td><td>1.5</td><td></td></tr>
<tr><td>Other vascular disorders</td><td></td><td></td></tr>
<tr><td>Placebo</td><td>0.9</td><td>1.15 (0.82,1.63)</td></tr>
<tr><td>Denosumab</td><td>1.1</td><td></td></tr>
<tr><td>Cardiovascular death</td><td></td><td></td></tr>
<tr><td>Placebo</td><td>1.1</td><td>0.79 (0.52,1.18)</td></tr>
<tr><td>Denosumab</td><td>0.9</td><td></td></tr>
</table>
[a] Safety analysis set

During the placebo-controlled phase of the pivotal study for MOP, adverse events in the cardiac disorders system organ class (SOC) were reported in 8 (6.7%) denosumab-treated and 3 (2.5%) placebo-treated subjects (note: 2 events of angina tonsillitis in the denosumab group were incorrectly coded to the cardiac disorders adverse event category. The incidence of adverse</td></tr>
</table>

	events in the vascular disorders SOC was 5.0% in denosumab-treated and 6.7% in placebo-treated subjects. In the GIOP study, adverse events in the cardiovascular disorders or vascular disorders SOC were reported in 65 (16.5%) denosumab-treated subjects and in 53 (13.8%) risedronate-treated subjects (HR [95% Cl]=1.27 [0.88, 1.82]). Subject incidence of serious adverse events in the cardiovascular or vascular SOC was 3.8% in the denosumab group, and 3.9% in the risedronate group. In Study 20190038 (a retrospective cohort study assessing the incidence of cardiovascular and cerebrovascular events among postmenopausal women and men with osteoporosis treated with denosumab or zoledronic acid for up to 36-months of treatment), the unadjusted incidence rates of myocardial infarction, stroke, and Ml-stroke composite outcome were 0.23 to 0.72 per 100 person-years. The differences in the unadjusted incidence rates of outcome between denosumab and zoledronic acid treatment groups were small (< 0.1 risk difference).
Severity	This risk has not been substantiated; however, cardiovascular events may be severe/life-threatening.
Reversibility	This risk has not been substantiated; however, effects of denosumab to block RANKL are fully reversible.
Long-term outcomes	This risk has not been substantiated; however, cardiovascular events could impact patient long-term outcome.
Impact on quality of life	Cardiovascular disease varies greatly in severity. For severe disease, patients may be hospitalized for treatment and disability may occur.
Risk factors and risk groups	The denosumab development program comprises studies of older subject populations (eg, osteoporosis, cancer) that are likely to have a higher incidence of pre-existing cardiovascular conditions and, thus, a higher incidence of cardiovascular toxicities than that of the general population (Schulz et al, 2004; Hak et al, 2000). Risk factors for atherosclerosis include age, sex, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes, and concomitant medications, including antipsychotic agents and COX-2 inhibitors (Murphy and Dargie, 2007; Smith et al, 2004).
Preventability	No preventive measures are known.
Impact on the risk-benefit balance of the product	The potential risk of cardiovascular events has been considered in the overall assessment supporting a positive benefit-risk profile.
Public health impact	Significant public health impact of Prolia on cardiovascular disease severity or incidence is not anticipated.

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

Table SVII.3.1.10 Important Potential Risk: Malignancy

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

	predisposition, and exposure to chemotherapy and radiation treatment (Anand et al, 2008; World Health Organization [WHO], 2010).
Preventability	No preventive measures are known.
Impact on the risk-benefit balance of the product	The potential risk of malignancy has been considered in the product benefit-risk assessment, which supports a positive benefit-risk profile in the indicated populations.
Public health impact	Significant public health impact is not anticipated.

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

SVII.3.2 Presentation of the Missing Information

There is no missing information for Osqay (based on the originator product Prolia, denosumab).

PART II: Module SVIII – Summary of Safety Concerns

Table SVIII.1 Summary of Safety Concerns

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

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection are presented in Table III.1.

Table III.1 Specific Adverse Reaction Follow-up Questionnaires

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

		with Osqay in the postmarketing environment

III.2 Additional Pharmacovigilance Activities

None.

III.3 Summary Table of Additional Pharmacovigilance Activities

Not applicable.

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

Not applicable.

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

Risk Minimisation Plan

V.1 Routine Risk Minimization Measures

Table V.1.1 Description of Routine Risk Minimisation Measures by Safety Concern

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

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

	• None.
Malignancy	Routine risk communication: • None Routine risk minimization activities recommending specific clinical measures to address the risk: • None.
Missing Information	
None	N/A

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

V.2 Additional Risk Minimization Measures

Table V.2.1 Additional Risk Minimization Measure: Patient Reminder Card

Objectives	Patient reminder cards will be provided to address the following risk (Annex 6): • Osteonecrosis of the jaw
Rationale for the additional risk minimization activity	The purpose of the patient reminder card is to remind patients about important safety information that they need to be aware of before and during treatment with denosumab (Osqay) injections for osteoporosis and bone loss, including: • the risk of osteonecrosis of the jaw during treatment with Osqay; • the need to highlight any problems with their mouth or teeth to their doctors/nurses before starting treatment; • the need to ensure good oral hygiene during treatment; • the need to inform their dentist of treatment with Osqay and to contact their doctor or dentist if problems with the mouth or teeth occur during treatment.
Target audience and planned distribution path	Target audience will be the patients. The patient reminder card will be distributed as per the approved dissemination plan agreed with each relevant national agency.
Plans to evaluate the effectiveness of the interventions and criteria for success	Monitor and evaluate postmarketing safety data and report in periodic safety update reports (PSURs). The distribution of the patient reminder card will be tracked to ensure that it is distributed in accordance with the dissemination plan agreed with each national agency. Additional requests for patient reminder cards and, where relevant 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 after introduction of the patient reminder card.

Evaluation of the effectiveness of risk minimization activities	No change in risk-benefit profile

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

V.3 Summary of Risk Minimization Measures

Routine and additional risk minimisation measures for Osqay mirror those of the reference product Prolia. These include SmPC warnings and the provision of a Patient Reminder Card for mitigation of osteonecrosis of the jaw. No deviations or new measures are proposed, as existing strategies are deemed sufficient based on post-marketing experience with the reference product.

Table V.3.1 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Hypocalcaemia	Routine risk minimisation measures: • SmPC Section 4.4 where recommendation regarding correction and monitoring of calcium levels is provided • SmPC Sections 4.2, 4.3 and 4.8 • PL Sections 2 and 4 Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for hypocalcaemia Additional pharmacovigilance activities: • None
Skin infection leading to hospitalisation	Routine risk minimisation measures: • SmPC Sections 4.4 and 4.8 • PL Sections 2 and 4 Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for infection Additional pharmacovigilance activities: • None
Osteonecrosis of the jaw	Routine risk minimisation measures: • SmPC Sections 4.4 where oral hygiene and dental management guidance is provided • SmPC Section 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for ONJ Additional pharmacovigilance activities: • None

Table V.3.1 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
	• PL Sections 2 and 4 Additional risk minimisation measures: • Patient reminder card (see Annex 6)	
Hypersensitivity reactions	Routine risk minimisation measures: • SmPC Section 4.3 and 4.8 • PL Sections 2 and 4 Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for hypersensitivity Additional pharmacovigilance activities: • None
Atypical femoral fracture	Routine risk minimisation measures: • SmPC Section 4.4 where recommendation for reporting potential symptoms is provided • SmPC Sections 4.8 • PL Sections 2 and 4 Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for AFF Additional pharmacovigilance activities: • None
Hypercalcemia in pediatric patients receiving denosumab and after treatment discontinuation	Routine risk minimisation measures: • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Important Potential Risks		

Table V.3.1 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Fracture healing complications	Routine risk minimisation measures: • SmPC Section 5.3 Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for fracture healing complications Additional pharmacovigilance activities: • None
Infection	Routine risk minimisation measures: • SmPC Section 4.8 • PL Section 4 Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for infection Additional pharmacovigilance activities: • None
Cardiovascular events	Routine risk minimisation measures: • None Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Malignancy	Routine risk minimisation measures: • None Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for malignancy Additional pharmacovigilance activities: • None
Missing Information		
None		

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

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

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

Summary of Risk Management Plan for Osqay® (denosumab)

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

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

This summary of the RMP for Osqay 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 Osqay's RMP.

I. The Medicine and What it is Used For

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

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

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Osqay, together with measures to minimize such risks and the proposed studies for learning more about Osqay'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 to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the public (e.g., with or without prescription) can help to minimize its risks.

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

In the case of Osqay, 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 Osqay is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Osqay 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 Osqay. 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 (e.g., on the long-term use of the medicine).

Table II.A.1 List of Important Risks and Missing Information

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

II.B Summary of Important Risks

Table II.B.1 Important Identified Risk: Hypocalcemia

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

Table II.B.2 **Important Identified Risk:** Skin infection leading to hospitalisation

Evidence for linking the risk to the medicine	This risk was identified in the phase 3, randomized, double-blind, placebo- or active-controlled studies for Prolia.
Risk factors and risk groups	Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), immunosuppressant drugs (e.g., corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition. Risk factors for skin infection in older patients include skin wounds, peripheral vascular disease, eczema/dermatitis, and venous stasis disorders.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections 4.4 and 4.8 • PL Sections 2 and 4 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None

Table II.B.3 Important Identified Risk: Osteonecrosis of the jaw

Evidence for linking the risk to the medicine	This risk was identified in open-label, long-term extensions to phase 3, randomized, double-blind, placebo-controlled studies for Prolia.
Risk factors and risk groups	Risk factors include duration of exposure to denosumab, prior bisphosphonate use (particularly for extended periods of time), older age, periodontal disease, dentoalveolar surgery, trauma from poorly fitting dentures, malignancy, chemotherapy, corticosteroids, smoking, systemic or regional infection, immune-compromised state predisposing to increased risk of infection, hypercoagulable state secondary to underlying malignancy, and vascular insufficiency due to thrombosis (Mehrotra and Ruggiero, *Hematology*, 2006;356-360*;* Ruggiero et al, *J Onco/ Pract*, 2006;2:7-14).
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4, where oral hygiene and dental management guidance is provided • SmPC Section 4.8 • PL Sections 2 and 4 Additional risk minimization measures: • Patient reminder card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None

Table II.B.4 Important Identified Risk: Hypersensitivity reactions

Evidence for linking the risk to the medicine	This risk was identified in the postmarketing setting based on a clinically plausible association between administration of denosumab and hypersensitivity events.
Risk factors and risk groups	Known hypersensitivity to denosumab and any of its excipients.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections 4.3, and 4.8 • PL Sections 2 and 4 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None

Table II.B.5 Important Identified Risk: Atypical femoral fractures

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

Table II.B.6 **Important Identified Risk:** Hypercalcemia in pediatric patients receiving denosumab and after treatment discontinuation

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

Table II.B.7 Important Potential Risk: Fracture healing complications

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

Table II.B.8 Important Potential Risk: Infection

Evidence for linking the risk to the medicine	This is considered a potential risk based on theoretical concerns which has not been substantiated in the extensive clinical study program or in the postmarketing experience.
Risk factors and risk groups	Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, HIV/AIDS, immunosuppressant drugs (e.g., corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.8 • PL Section 4 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None

Table II.B.9 Important Potential Risk: Cardiovascular events

Evidence for linking the risk to the medicine	This is a theoretical risk based on epidemiological data demonstrating elevated osteoprotegerin in patients with cardiovascular disease.
Risk factors and risk groups	The denosumab development program comprises studies of older subject populations (e.g., 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 Vase Biol*, 2000;20:1926-1931). Risk factors for atherosclerosis include age, sex, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes, and concomitant medications, including antipsychotic agents and COX-2 inhibitors (Murphy and Dargie, *Drug Safety*, 2007;30[9]:783-804; Smith et al, *Circulation*, 2004;109[21]:2613-2616).
Risk minimisation measures	Routine risk minimisation measures: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None

Table II.B.10 Important Potential Risk: Malignancy

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

II.C Post-Authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions to the marketing authorisation or specific obligation for Osqay.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for Osqay.

PART VII: ANNEXES

Annex 4 – Specific adverse drug reaction follow-up forms

Specific adverse reaction targeted follow-up questionnaires for Osqay are available for the following topics:

- Hypocalcaemia
- Infections
- Osteonecrosis of the jaw
- Hypersensitivity reactions
- Atypical femoral fractures
- Fracture healing complications
- Malignancy

Theramex **DENOSUMAB Core Questionnaire**
Hypocalcemia

AER #

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

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

Patient Identifier

Patient Initials

Date of Event Onset

Date of This Report

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

Age at time of event: _____

Event Reported Term

Study No.

☐ Clinical Trial
☐ Post-marketing

Safety Database No.

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

Denosumab Indication

☐ Postmenopausal osteoporosis

☐ Bone loss from hormone ablation therapy

Please specify diagnosis _____

☐ Advanced cancer with bone metastasis

Please specify cancer _____

☐ Other

Please specify _____

☐ Don't know

Denosumab Dose

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

☐ Other Please specify _____

☐ Don't know

Denosumab Exposure

Denosumab first administered (date) _____

Last denosumab dose before event (date)

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

If yes, please specify _____

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

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

SIGNS AND SYMPTOMS (Check all that apply)

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

☐ Convulsions ☐ Muscle twitching

☐ Muscle cramping ☐ Paresthesia

☐ Syncope ☐ Tetany

☐ None ☐ Other _____

DIAGNOSIS (Check all that apply)

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

Please provide serum albumin result _____

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

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

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

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

TREATMENT

Treated only as an outpatient? ☐ Yes ☐ No

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

Treated in the ER? ☐ Yes ☐ No

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

Treatment included general hospital admission for calcium replacement?

☐ Yes ☐ No ☐ Unknown

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

Treatment included ICU admission? ☐ Yes ☐ No ☐ Unknown

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

Overall length of hospital stay:

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

Anti-arrhythmic medications? ☐ Yes ☐ No ☐ Unknown

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

Anti-arrhythmic medications _____

Other treatment? ☐ Yes ☐ No ☐ Unknown

If yes, specify: _____

REPORTER Name:

Address:

City: State/

Country: Province:

Email: Postal Code:

Phone: (include country code)

Signature _____

Title _____ **Date** _____

CONTINUED ON NEXT PAGE

Theramex **DENOSUMAB Core Questionnaire**
Hypocalcemia

AER #

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

Patient Identifier | Patient Initials | Safety Database No.

RISK FACTORS (Check all that apply)

Medical History Risk Factors

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

If yes, please provide dates and details:

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

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

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

Medication Risk Factors

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

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

Concomitant Medications

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

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

Other concomitant medications _____

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

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

Theramex **DENOSUMAB Core Questionnaire Infection**

AER #

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

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

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

Gender: ☐ Male ☐ Female Weight: __lb __kg Age at time of event: __

Study No. ______ ☐ Clinical Trial ☐ Post-marketing

Event Reported Term ______

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 mos ☐ 120 mg SC every 4 wks

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

Denosumab Exposure: Denosumab first administered (date) ______

Last denosumab dose before event (date) ______

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

If yes, please specify ______

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

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

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

☐ Fever ______

☐ Cough ______

☐ Swelling ______

Location ______

☐ Shortness of breath ______

☐ Pain ______

Location ______

☐ Rash ______

Location ______

☐ Prolonged fatigue ______

☐ Diarrhea ______

☐ Discharge ______

Location ______

Description ______

☐ Chills ______

☐ Night sweats ______

☐ Other ______

☐ Organ system affected:

☐ Cardiac

☐ Ear/nose

☐ Throat

☐ Gastrointestinal

☐ Respiratory

☐ Musculoskeletal (including joints)

☐ Nervous (cerebrospinal fluid)

☐ Skin Location ______

☐ Kidney/genito-urinary

☐ Systemic (bacteremia and/or sepsis)

☐ Other ______

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

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

CONTINUED ON NEXT PAGE

Theramex

DENOSUMAB Core Questionnaire Infection (continued)

AER #

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

Patient Identifier	Patient Initials	Safety Database No.

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

CHECK WHICH INFECTION APPLIES

- ☐ Cardiac infections
  - ☐ Endocarditis _____
  - ☐ Pericarditis (purulent; tuberculous) _____
  - ☐ Other, please specify: _____
- ☐ Ear and labyrinth infections
  - ☐ Otitis media _____
  - ☐ Otitis externa _____
  - ☐ Other, please specify: _____
- ☐ Gastrointestinal/abdominal infections
  - ☐ Colitis _____
  - ☐ Diverticulitis _____
  - ☐ Appendicitis _____
  - ☐ Abdominal sepsis (including peritonitis) _____
  - ☐ Hepatic abscess _____
  - ☐ Hepatitis B _____
  - ☐ Hepatitis C _____
  - ☐ Other, please specify: _____
- ☐ Musculoskeletal and connective tissue infections
  - ☐ Osteomyelitis _____
  - ☐ Septic arthritis _____
  - ☐ Other, please specify: _____
- ☐ Nervous system infections
  - ☐ Meningitis _____
  - ☐ Encephalitis _____
  - ☐ Other, please specify: _____
- ☐ Respiratory tract infections
  - ☐ Pneumonia _____
  - ☐ Pulmonary TB _____
  - ☐ Lung abscess _____
  - ☐ Legionnella pneumonia _____
  - ☐ Mycoplasma pneumonia _____
  - ☐ Other, please specify: _____
- ☐ Kidney and genito-urinary tract infections
  - ☐ Cystitis _____
  - ☐ Pyelonephritis _____
  - ☐ Urinary tract infection _____
  - ☐ Other, please specify: _____
- ☐ Systemic infections
  - ☐ Bacteremia _____
  - ☐ Sepsis _____
  - ☐ Toxic shock syndrome _____
  - ☐ Other, please specify: _____
- ☐ Wound and skin infections
  - ☐ Cellulitis _____
  - ☐ Erysipelas _____
  - ☐ Necrotizing fasciitis _____
  - ☐ Abscess _____
  - ☐ Other skin infections, please specify: _____
- ☐ Opportunistic infections
  - ☐ Aspergillus (invasive forms only) _____
  - ☐ Blastomycosis pulmonary or extra-pulmonary infections _____
  - ☐ Candidiasis systemic _____
  - ☐ Coccidioidemycosis secondary/systemic _____
  - ☐ Cryptococcal infection – pulmonary and non-pulmonary _____
  - ☐ Cytomegalovirus – include systemic site _____
  - ☐ Herpes simplex (meningitis or encephaltitis) _____
  - ☐ Herpes zoster (only systemic or disseminated: involving 2 or more dermatomes) _____
  - ☐ Histoplasma infections - chronic disseminated or severe acute _____
  - ☐ Mucormycosis (=zygomycosis) including infections due to Rhizopus, Mucor and Absidia of lung, genito-urinary tract, kidney, GIT, skin _____
  - ☐ Mycobacterium tuberculosis _____
  - ☐ Non-tuberculosis mycobacterium _____
  - ☐ Nocardia infection – of brain, lungs, kidney, skin _____
  - ☐ Paracoccidioides infections of lungs, skin other _____
  - ☐ Pneumocystis carinii pneumonia _____
  - ☐ Sporotrichosis – disseminated infections _____
  - ☐ Toxoplasmosis encephalitis or disseminated _____
  - ☐ Other opportunistic infections, please specify: _____
- ☐ Other infections, please specify: _____
- ☐ Parasitic evaluation (ova, etc.) _____

REPORTER

Name:

Address:

City: State/ Province:

Country: Postal Code:

Email:

Phone: (include country code)

Signature _____

Title _____ **Date** _____

CONTINUED ON NEXT PAGE

Theramex

DENOSUMAB Core Questionnaire
Infection (continued)

AER #

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

Patient Identifier | Patient Initials | Safety Database No.

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

DIAGNOSTICS

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

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

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

TREATMENT

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

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

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

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

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

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

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

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

Theramex 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: _____

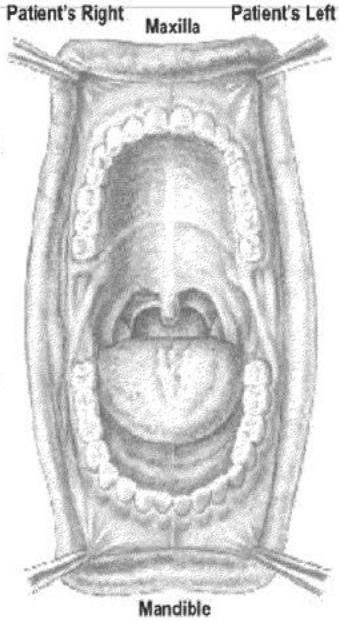
Oral Findings

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 _____

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) _____

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

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

REPORTER Name:

Address:

City: State/ Province:

Country: Postal Code:

Email:

Phone: (include country code)

Signature _____

Title _____ **Date** _____

CONTINUED ON NEXT PAGE

Theramex **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

Patient Reminder Card Status (For EU Patients)

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

CONTINUED FROM PREVIOUS PAGE

Theramex **DENOSUMAB Core Questionnaire HYPERSENSITIVITY**

AER #		

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

Patient Identifier

Patient Initials

Date of Event Onset

Date of This Report

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

Age at time of event: _____

Event Reported Term

Study No.

☐ Clinical Trial
☐ Post-marketing

Safety Database No.

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

Denosumab Indication:

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

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

Denosumab Exposure:

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

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

SIGNS AND SYMPTOMS (Check all that apply)

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

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

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

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

CONTINUED ON NEXT PAGE

Theramex **DENOSUMAB Core Questionnaire HYPERSENSITIVITY (continued)**

AER #

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

Patient Identifier | Patient Initials | Safety Database No.

TREATMENT (Please provide dates and indicate attachments if available)

☐ ER corticosteroids
Route: ☐ IV ☐ oral

☐ ER anti-histaminics
Route: ☐ IV only ☐ oral only ☐ both oral and IV

☐ Required hospital admission ☐ Yes ☐ No
Overall length of hospital stay
☐ < 1 day ☐ > 1 day or < 7 days ☐ > 7 days

☐ ICU admission ☐ Yes ☐ No ☐ Unknown
Overall length of hospital stay
☐ < 1 day ☐ > 1 day or < 7 days ☐ > 7 days

☐ In-hospital corticosteroids
Route: ☐ IV only ☐ oral only ☐ both oral and IV

☐ In-hospital anti-histaminics
Route: ☐ IV only ☐ oral only ☐ both oral and IV

☐ Other in-hospital treatment
☐ IV vasopressors ☐ Yes ☐ No ☐ Unknown
☐ Intubation/mechanical ventilation ☐ Yes ☐ No ☐ Unknown

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

_____

_____

_____

_____

_____

_____

_____

CONCOMITANT MEDICATIONS

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

☐ Anticonvulsants (check which apply):
- ☐ Phenytoin
- ☐ Carbamazepine
- ☐ Phenobarbital

☐ Antibiotics (check which apply):
- ☐ Beta-lactams including penicillin and cephalosporin
- ☐ Macrolides
- ☐ Sulfonamides
- ☐ Quinolones

☐ Hypersensitivity event resolved ☐ Yes ☐ No ☐ Unknown
If yes, date (DD/MM/YYYY): _____

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

☐ Other consult report (please indicate any attachments) _____

_____

_____

_____

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

Theramex

DENOSUMAB Core Questionnaire
MARKETING 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)

Theramex

DENOSUMAB Core Questionnaire

POSTMARKETING REPORTS OF POTENTIAL ATYPICAL FRACTURE

(low energy, subtrochanteric/femoral shaft fractures)

AER #

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

PATIENT / CASE ADMINISTRATIVE INFORMATION (Please indicate 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** _____

Theramex **DENOSUMAB Core Questionnaire FRACTURE HEALING**

AER #

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

Patient Identifier

Patient Initials

Date of Event Onset

Date of This Report

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

Age at time of event: _____

Event Reported Term

Study No.

☐ Clinical Trial
☐ Post-marketing

Safety Database No.

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

Denosumab Indication:

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

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

Denosumab Exposure:

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

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

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

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

Specify location (check all that apply):

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

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

Specify location (check all that apply):

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

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

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

Characteristics of fracture (check all that apply):

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

CONTINUED ON NEXT PAGE

Theramex **DENOSUMAB Core Questionnaire FRACTURE HEALING (continued)**

AER #

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

Patient Identifier	Patient Initials	Safety Database No.

TREATMENT (Please provide dates and indicate attachments if available)

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

☐ Casting _____ ☐ Surgery _____

☐ Non-surgical reduction _____ ☐ Traction _____

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

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

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

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

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

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

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

☐ Current smoker/tobacco use _____

☐ History or current corticosteroid use _____

☐ Prior fracture history _____

☐ Diabetes _____

REPORTER

Name:

Address:

City:

State/ Province:

Postal Code:

Country:

Email:

Phone: (include country code)

Signature _____

Title _____ **Date** _____

Office Patient Identifier _____ Patient Initials _____ Theramex AER No. _____

Questionnaire for Malignancy Adverse Events

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

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

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

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

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

Tumor stage, if known: _____

Primary site of malignancy: _____

Tumor Stage:

Tumor Size (Check which one applies):

TX ☐ T0 ☐ Tis ☐ T1 ☐ T2 ☐ T3 ☐ T4 ☐

Tumor Grade (Check which one applies):

GX ☐ G1 ☐ G2 ☐ G3 ☐

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

(If yes, skip next 2 questions)

Lymph Node Involvement (Check which one applies):

NX ☐ N1 ☐ N2 ☐ N3 ☐

Metastases (Check which one applies):

MX ☐ M0 ☐ M1 ☐

TREATMENT:

Hospitalized? Yes ☐ No ☐ Unknown ☐

ICU admission? Yes ☐ No ☐ Unknown ☐

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

Surgical treatment? Yes ☐ No ☐ Unknown ☐

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

Hormonal treatment? Yes ☐ No ☐ Unknown ☐

Radiation treatment? Yes ☐ No ☐ Unknown ☐

Bone marrow transplant? Yes ☐ No ☐ Unknown ☐

If yes, autologous ☐ heterologous ☐

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

RISK FACTORS (Check all that apply):

Smoking ☐

Prior Malignancy ☐

Positive Family History (Check all that apply):

Same cancer ☐

Different cancer ☐

Prior therapeutic radiation exposure ☐

Environmental exposure ☐

Specify: _____

Annex 6 – Details of proposed additional risk minimization activities (if applicable)

Approved key messages of the additional risk minimization measures

Patient reminder card:

Patient Reminder Cards for osteonecrosis of the jaw (ONJ) will be distributed according to the dissemination plan agreed with, and approved by, each relevant national agency with background information on the purpose of the patient reminder card.

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

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