RISK MANAGEMENT PLAN (RMP) for DENOSUMAB

RMP Version number	0.2
Data lock point for this RMP	01st January 2026
Date of final sign off	
Rationale for submitting an updated RMP	Not applicable - Initial marketing authorisation application
Summary of significant changes in this RMP	Not applicable - Initial marketing authorisation application
Other RMP versions under evaluation	Not applicable
Details of the currently approved RMP	Not applicable
QPPV name	Mikolaj Cwik
QPPV signature	

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ABBREVIATIONS

Abbreviation	Definition
AAC	Area Above the Curve
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AUC	Area Under the Curve
ATC	Anatomical Therapeutic Chemical
AFF	Atypical Femoral Fracture
AST	Aspartate Aminotransferase
BMI	Body Mass Index
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
DLP	Data Lock Point
ECG	Electrocardiogram
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EEA	European Economic Area
EU-RMP / EU RMP	European Union Risk Management Plan
GCTB	Giant Cell Tumour of Bone
HIV	Human Immunodeficiency Virus
ICH	International Council for Harmonisation
IgG	Immunoglobulin G
INN	International Nonproprietary Name
MAH	Marketing Authorisation Holder
MDRD	Modification of Diet in Renal Disease
NOAEL	No Observed Adverse Effect Level
NPM	New Primary Malignancy
NYHA	New York Heart Association
OPG	Osteoprotegerin
ONJ	Osteonecrosis of the Jaw
PTH	Parathyroid Hormone
PIL	Patient Information Leaflet
PK	Pharmacokinetics
PIL	Patient Information Leaflet
PMGCTB	Primary Malignancy in Giant Cell Tumour of Bone
Q4W	Once every 4 Weeks
QPPV	Qualified Person for Pharmacovigilance
RA	Rheumatoid Arthritis
RANKL	Receptor Activator of Nuclear Factor Kappa-B Ligand
RMP	Risk Management Plan
SC	Subcutaneous
SmPC	Summary of Product Characteristics
TEAE	Treatment-Emergent Adverse Event
uNTx/Cr	Creatinine adjusted urinary N-telopeptide
VPC	Ventricular Premature Complex

PART I: PRODUCT OVERVIEW

Table Part I.1 – Product Overview

Active substance(s) (INN or common name)	denosumab
Pharmacotherapeutic group(s) (ATC Code)	Drugs for treatment of bone diseases – other drugs affecting bone structure and mineralisation ATC code: M05BX04
Marketing Authorisation Applicant	Ascend GmbH Pollux Business Center GmbH, Sebastian-Kneipp Straße 41, 60439 Frankfurt am Main Germany
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Denosumab Ascend 120 mg solution for injection
Marketing authorisation procedure	Decentralised procedure
Brief description of product	**Chemical class:** Fully human monoclonal antibody of the immunoglobulin G (IgG) subclass
	Summary of mode of action: RANKL exists as a transmembrane or soluble protein. RANKL is essential for the formation, function and survival of osteoclasts, the sole cell type responsible for bone resorption. Increased osteoclast activity, stimulated by RANKL, is a key mediator of bone destruction in metastatic bone disease and multiple myeloma. Denosumab is a human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to RANKL, preventing the RANKL/RANK interaction from occurring and resulting in reduced osteoclast numbers and function, thereby decreasing bone resorption and cancer-induced bone destruction. Giant cell tumours of bone are characterised by neoplastic stromal cells expressing RANK ligand and osteoclast-like giant cells expressing RANK. In patients with giant cell tumour of bone, denosumab binds to RANK ligand, significantly reducing or eliminating osteoclast-like giant cells. Consequently, osteolysis is reduced and proliferative tumour stroma is replaced with non-proliferative, differentiated, densely woven new bone.

	Important information about its composition: Denosumab is a full-length human monoclonal antibody derived using genetically engineered mammalian (Chinese hamster ovary) cells. Excipient with known effects Each 1.7 mL of solution contains 78.2 mg sorbitol.
Hyperlink to the Product Information	Refer Module 1.3.1
Indication(s) in the EEA	Current: Prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with advanced malignancies involving bone. Treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.
	Proposed (if applicable): None
Dosage in the EEA	Current: *Prevention of skeletal related events in adults with advanced malignancies involving bone* The recommended dose is 120 mg administered as a single subcutaneous injection once every 4 weeks into the thigh, abdomen or upper arm. *Giant cell tumour of bone* The recommended dose of Denosumab Ascend is 120 mg administered as a single subcutaneous injection once every 4 weeks into the thigh, abdomen or upper arm with additional 120 mg doses on days 8 and 15 of treatment of the first month of therapy.
	Proposed (if applicable): None
Pharmaceutical form and strength	Current: Solution for injection 120 mg of denosumab in 1.7 mL of solution (70 mg/mL)
	Proposed (if applicable): None
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II: SAFETY SPECIFICATION

MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

This module is not applicable for biosimilar medicinal products.

MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

SII.1. Key safety findings from non-clinical studies and relevance to human usage:

Ascend has completed repeated dose toxicology study comparing Denosumab Ascend to the RMP (Prolia) according to current testing guideline standards and regulatory requirements to support the intended use of Denosumab Ascend. In accordance with the use in humans, the chosen route of administration in the animal study was subcutaneous injections. Two comparative 28-day repeated dose subcutaneous toxicity studies were performed to assess the sub-acute toxicity of Biosimilar Denosumab, one in Sprague Dawley rats and the other in New Zealand White Rabbits.

The terms Denosumab Ascend and ENZ215 may be used interchangeably in this document.

Key safety findings (from non-clinical studies)	Relevance to human usage:
Repeat-dose toxicity of Denosumab Ascend: **Sprague Dawley Rats**: The treatment with Denosumab from Ascend at the dose levels of 62 mg/kg body weight/week of rats had no noteworthy effects on general health of the animals, body weight, net body weight gains, feed consumption, immunogenicity, hematology, clinical chemistry, serum electrolytes, urine parameters, fasting body weights, macro and microscopic lesions in both sexes at all treated groups In view of the results observed, the evaluated No Observed Adverse Effect Level (NOAEL) was 62 mg/kg body weight/week on repeated 28 subcutaneous administrations to rats under the test conditions and doses employed. **New Zealand White Rabbits:** The treatment with Denosumab from Ascend at the dose levels of 31 mg/kg body weight/week of rabbits had no noteworthy effects on general health of the animals, body weight, net body weight gains, feed consumption, immunogenicity, hematology, clinical chemistry, serum electrolytes, urine parameters, fasting body weights, macro and microscopic lesions in both sexes at all treated groups In view of the results observed, the evaluated NOAEL is 31 mg/kg body weight/week on repeated 28 subcutaneous administrations to rats under the test conditions and doses employed.	No direct safety concern for the use of denosumab in the target population.

Key safety findings (from non-clinical studies)	Relevance to human usage:
Repeat-dose toxicity of Xgeva (European Public Assessment Report [EPAR]) In monkey, subcutaneous doses up to 10 mg/kg once weekly and 50 mg/kg given once per month were administered for durations up to 12 months. No specific single dose toxicity studies were conducted, but no remarkable observations were recorded after the first dose in the repeated dose toxicity studies. The intended human dose is 120 mg given subcutaneously every 4 weeks corresponding to an AUC 0-4 weeks of 752 µg*day/ml and in most cases doses used in toxicology studies represented high multiples of expected human exposure. However, the development of neutralising and/or binding antibodies in subsets of animals, resulting in greatly reduced exposure, was a confounding factor. There were no remarkable changes in clinical parameters, serum biochemistry, or histopathological effects in any of the studies, but bone turnover markers in serum and urine were decreased as were calcium levels (in males). Clinical data indicate cataracts as common eye disorders, but no treatment related ocular changes were reported after ophthalmological examinations in monkey. In the 12-month monkey study, 2 deaths at the high dose occurred. The overall conclusion was that deaths were not related to treatment, one diagnosed with possibly cardiac inflammation and the other death linked to acute exacerbation of pre-existing parasitic intestinal infection. However, it does not seem completely justified to exclude a possibility of involvement of an induced dysregulation of immune function in these findings. Of note is that the 2 deaths were both males. No deaths were recorded in the 16-month bone study that utilized female animals only.	
Reproductive/Developmental toxicity of Denosumab Ascend Reproductive toxicology studies have not been performed because they are not required according to the EMA guidance on similar biological medicinal products containing biotechnology-derived proteins as active substance: nonclinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1) and EMA guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010).	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 with denosumab. It is not known if denosumab is excreted in human milk. Because denosumab has the

Key safety findings (from non-clinical studies)	Relevance to human usage:
Reproductive/Developmental toxicity of Xgeva (RMP) Denosumab had no effect on female fertility or male reproductive organs in monkeys at exposures that were 9.5- to 16-fold higher, respectively, than the human exposure at 120 mg SC administered once Q4W. In a study of cynomolgus monkeys dosed with denosumab during the period equivalent to the first trimester at area above the curve (AAC) exposures up to 10-fold higher than the human dose (120 mg Q4W), there was no evidence of maternal or foetal harm. In this study, foetal lymph nodes were not examined. In another study of cynomolgus monkeys dosed with denosumab throughout pregnancy at AAC exposures 12-fold higher than the human dose (120 mg every 4-weeks), there were increased stillbirths and postnatal mortality; abnormal bone growth resulting in reduced bone strength, reduced haematopoiesis, and tooth malalignment; absence of peripheral lymph nodes; and decreased neonatal growth. There was no evidence of maternal harm prior to labour; adverse maternal effects occurred infrequently during labour. Maternal mammary gland development was normal. Denosumab has been shown to be a potent inhibitor of bone resorption by inhibition of RANKL. Adolescent primates dosed with denosumab at 2.8 and 15 times (10 and 50 mg/kg dose) the clinical exposure based on AAC had abnormal growth plates. In neonatal cynomolgus monkeys exposed in utero to denosumab at 50 mg/kg, there was increased postnatal mortality; abnormal bone growth resulting in reduced bone strength, reduced haematopoiesis, and tooth malalignment; absence of peripheral lymph nodes; and decreased neonatal growth. Following a recovery period from birth out to 6 months of age, the effects on bone largely returned to normal; there were no adverse effects on tooth eruption; and minimal to moderate mineralization in multiple tissues was seen in one recovery animal. In neonatal rats, inhibition of RANKL (target of denosumab therapy) was associated with inhibition of bone growth, altered growth plates, and inhibited tooth eruption, and these changes were partially reversible upon cessation of RANKL inhibition.	potential to cause adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug. Use in pregnant and lactating women is not considered a safety concern in this RMP. The safety and efficacy of denosumab have not been established in paediatric patients other than skeletally mature paediatric patients with GCTB. Treatment with denosumab may impair bone growth in children with open growth plates and may inhibit eruption of dentition.

Key safety findings (from non-clinical studies)	Relevance to human usage:
Genotoxicity/Carcinogenicity of Denosumab Ascend Genotoxicity/carcinogenicity studies have not been performed because they are not required according to the EMA guidance on similar biological medicinal products containing biotechnology-derived proteins as active substance: nonclinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1) and EMA guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010). **Genotoxicity/Carcinogenicity of Xgeva (EPAR)** No studies were conducted. Denosumab is a recombinant protein and contains no inorganic or synthetic organic linkages or other non-protein portions. Regulatory guidance is consistent with studies on genotoxicity not being necessary for this type of product. No carcinogenicity studies were conducted in accordance with available regulatory guidance. Ovariectomized monkey treated for up to 16 months with denosumab showed no evidence of pre neoplastic lesions. However, potential to interfere with the immune system cannot be discounted. The multiple signalling pathways involved in OPG effects, and by analogy possibly also relevant in the case of denosumab, indicate a potential for dysregulation of functions that could be critical in e.g. cancer pathogenesis.	Not applicable
General Safety Pharmacology of Denosumab Ascend No specific safety pharmacology studies were performed. Safety end-points were incorporated into the repeat-dose toxicity study. This approach is compatible with the EMA guidance on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues EMEA/CHMP/BMWP/42832/2005 Rev1) and EMA guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010). **General Safety Pharmacology of Xgeva (EPAR)** The safety pharmacology package included two studies; one of these was incorporated in a toxicology study in accordance with ICH S6 and ICH S7A. According to the guideline, clinical observation of animals is generally not adequate to assess	Not applicable

Key safety findings (from non-clinical studies)	Relevance to human usage:
respiratory function. However, since no indication of denosumab to affect respiratory function were noted, the assessment in toxicology study is considered sufficient. There was no ECG evidence of cardiotoxicity after 53 weeks of treatment with denosumab. Isolated cases of slight bradycardia, fused P-T wave or slight tachycardia were observed in single animals. These findings were not considered to be related to the administration of the test material. Two male animals died in the high dose group. According to the Applicant these deaths were not related to treatment. In other study, one animal (3 mg/kg) had a run of four ventricular premature complexes (VPCs) approximately 45 minutes following administration of the test article. This episode was not considered to be related to treatment with denosumab. No treatment related changes in respiration rate were observed. No treatment related cage side observations were observed.	
Mechanisms for Drug Interactions of Denosumab Ascend Drug Interactions studies have not been performed because they are not required according to the EMA guidance on similar biological medicinal products containing biotechnology-derived proteins as active substance: nonclinical and clinical issues EMEA/CHMP/BMWP/42832/2005 Rev1) and EMA guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010). **Mechanisms for Drug Interactions of Xgeva (EPAR)** No specific preclinical studies have been conducted addressing drug interactions. In the switch study performed in ovariectomized cynomolgus monkeys with 6 months pretreatment of alendronate before 6 months treatment of denosumab (report 106564) no adverse effects on the pharmacodynamic activity of either alendronate or denosumab were noted. The absence of pharmacodynamic drug interaction studies is considered acceptable.	Not applicable

Key safety findings (from non-clinical studies)	Relevance to human usage:
Juvenile Toxicity Studies of Denosumab Ascend Juvenile toxicity studies have not been performed because they are not required according to the EMA guidance on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1) and EMA guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010). **Juvenile Toxicity Studies of Xgeva (EPAR)** No specific studies were conducted.	Not applicable

Conclusion: Non-clinical studies did not reveal any safety findings of concern.

MODULE SIII - CLINICAL TRIAL EXPOSURE

The Enzene teriparatide clinical development programme consists of the following clinical studies:

ALK22/ENZ215-DEN1: A randomized, double-blind, three-arm, parallel-group, single-dose study to compare the pharmacokinetics, pharmacodynamics, safety, tolerability, and immunogenicity of Denosumab (ENZ215, EU-sourced Prolia®, and US-sourced Prolia®) in healthy adult male volunteers. A total of 207 subjects were randomized in the study. Sixty-Eight (68) subjects received ENZ215, Seventy (70) subjects received US approved Prolia and Sixty-Nine (69) received EU approved Prolia. The study duration was approximately 28 months (ie, 18 months of recruitment period, 4 weeks of screening period and approximately 39 weeks [270 days] of study period).

ALK22/ENZ215-DEN2: A Phase 3, Randomised, Double-blind, Parallel-group, Active-controlled Study to Compare the Efficacy, Safety, Pharmacodynamics, Pharmacokinetics and Immunogenicity of Enzene Denosumab (ENZ215) and Prolia® in Postmenopausal Women with Osteoporosis. A total of 504 subjects were randomized in the study. 253 subjects received ENZ215, and 251 received EU approved Prolia. The study was divided into three periods: Screening period: up to 35 days; Double-blind treatment period of 12 months; and Open-label, switch-over period of six months. All eligible participants were randomised in the double-blind treatment period in a 1:1 ratio to receive either ENZ215 or Prolia® (60 mg) SC on Day 1 and Month 6. A PK sub-study was conducted in a subset of 120 participants with 60 participants in each arm. All participants randomised to the double-blind treatment period (except for a subset of participants described hereafter) who completed the study at Month 12. A subset of 120 participants randomised to Prolia arm and who completed 12 months of the double-blind treatment period without any significant safety concerns per the Investigator's discretion were offered to enroll in the open-label, switch-over extension period. After reconsenting for the open-label, switch-over study, the participants were re-randomised in a 1:1 ratio to receive either ENZ215 or Prolia® (60 mg) SC at Month 12. These participants completed the study at Month 18.

Following data is from study ENZ215-DEN2 conducted in postmenopausal women with osteoporosis; no clinical trials in patients with malignancies involving bone have been conducted in the clinical development of ENZ215.

Duration of exposure:

Double-blind treatment period: Of the total 504 randomised and treated participants, the majority of the participants (94.8%) received two injections of study treatment during the double-blind treatment period: 237 participants (93.7%) in the ENZ215 group and 241 participants (96.0%) in the Prolia group. The remaining participants received only one injection: 16 participants (6.3%) in the ENZ215 group and 10 participants (4.0%) in the Prolia group.

Table SIII.1: Duration of exposure

Indication: Postmenopausal osteoporosis				
	ENZ215		**Prolia®**	
Duration of exposure	**Patients**	**Person time**	**Patients**	**Person time**
Less than 182 days	16	2,896	10	1,810
182 days to 362 days	237	85,794	241	87,242
Total person time for indication	253	88,690	251	89,052

Table SIII.2: Age group and gender

	Patients	
Age group	**ENZ215**	**Prolia®**
≥ 55 to < 70 years	171	171
≥ 70 to ≤ 85 years	82	80
Total	253	251

Note: All the subjects were exposed to Denosumab in this study were females

Table SIII.3: Dose

	ENZ215		Prolia®	
Dose	**Patients**	**Person time**	**Patients**	**Person time**
60 mg	16	2,896	10	1,810
120 mg	237	85,794	241	87,242
Total person time for indication	253	88,690	251	89,052

Table SIII.4: Ethnic origin

	Patients	
Ethnic origin	**ENZ215**	**Prolia®**
Hispanic or Latino	0	1
Not Hispanic or Latino	253	250
Unknown	0	0
Total	253	251

Open-label extension period: All 120 participants (100.0%) who entered the open-label extension period received one injection of study treatment during the open-label extension period.

Table SIII.5: Duration of exposure

Indication: Postmenopausal osteoporosis				
	ENZ215		Prolia®	
Duration of exposure	**Patients**	**Person time**	**Patients**	**Person time**
Less than 182 days	60	10,860	60	10,860
Total person time for indication	60	10,860	60	10,860

Table SIII.6: Age group and gender

	Patients	
Age group	**ENZ215**	**Prolia®**
≥ 55 to < 70 years	40	41
≥ 70 to ≤ 85 years	20	19
Total	60	60

Note: All the subjects were exposed to Denosumab in this study were females

Table SIII.7: Dose

	ENZ215		Prolia®	
Duration of exposure	**Patients**	**Person time**	**Patients**	**Person time**
60 mg	60	10,860	60	10,860
Total person time for indication	60	10,860	60	10,860

Table SIII.8: Ethnic origin

	Patients	
Ethnic origin	**ENZ215**	**Prolia®**
Hispanic or Latino	0	1
Not Hispanic or Latino	60	59
Unknown	0	0
Total	60	60

MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

The important exclusion criteria from the pivotal clinical study are presented below.

Patient who has previously received denosumab (Prolia, Xgeva, or biosimilar denosumab), any other monoclonal antibodies (e.g., romosozumab), or biologic agents for osteoporosis. Receipt of any investigational drug within 4 weeks or five half-lives (whichever is longer) prior to the first administration of the study drug

Reason for exclusion: The above-mentioned exclusion criteria were applied to prevent misinterpreting observations about study-related treatment that were actually received due to prior therapies.

Is it considered to be included as missing information?: No

Rationale: Patients with above mentioned criteria were excluded to prevent interference with efficacy and safety study endpoints.

Patient with a hypersensitivity to any component of denosumab.

Reason for exclusion: Patients with hypersensitivity to any component of the medicinal products were excluded from the clinical development programme for safety reasons. Patients with a known hypersensitivity would be at a higher risk of subsequent serious systemic, potentially life-threatening hypersensitivity reactions with re-exposure.

Is it considered to be included as missing information?: No

Rationale: The use of denosumab is contraindicated in patients with a known hypersensitivity to the active substance or to any of the excipients. This is adequately described in the SmPC of Denosumab Ascend (Section 4.3 [Contraindication] and Section 4.8 [Undesirable effects]).

Patient has one of the following laboratory test results at Screening:

a) Serum 25-OH vitamin D<20 ng/mL (Patients can be enrolled if a repeat test (post supplementation) prior to enrollment shows corrected 25 (OH) vitamin D level ≥ 20 ng/mL (≥ 50 nmol/L).)

b) Estimated glomerular filtration rate <45 mL/min/1.73 m2 by the Modification of Diet in Renal Disease (MDRD) formula

Reason for exclusion: 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 to prevent hypocalcaemia. The rationale for exclusion of patients with severe renal dysfunction is because these patients have disordered calcium metabolism, and are at risk of early termination.

Is it considered to be included as missing information?: No

Rationale: The use of denosumab is contraindicated in patients with hypocalcaemia. This is adequately described in the SmPC of Denosumab Ascend (Section 4.3 [Contraindication] and

Section 4.8 [Undesirable effects]). Patients with severe renal impairment (creatinine clearance <30 mL/min) or receiving dialysis are at greater risk of developing hypocalcaemia. The risk of developing hypocalcaemia and accompanying elevations in parathyroid hormone increases with increasing degree of renal impairment. Regular monitoring of calcium levels is especially important in these patients. This is adequately described in the SmPC of Denosumab Ascend (Section 4.4 [Special warnings and precautions for use]).

Concurrent or past history of infection with active hepatitis B or hepatitis C or human immunodeficiency virus (HIV). However, a patient with past hepatitis B was allowed if resolved.

Concurrent or past history of any active infection for which systemic anti-infectives were used within 4 weeks prior to randomization b. A serious infection defined as requiring hospitalization or intravenous anti-infectives within 8 weeks prior to randomization.

Reason for exclusion: Treatment with immunomodulatory agents may increase the risk of infection or worsen an existing infection. Such infections may confound safety evaluation. Moreover, infectious disease may lead to increased risk of dropout.

Is it considered to be included as missing information?: No

Rationale: Patients with above mentioned conditions were excluded to prevent interference with efficacy and safety study endpoints.

Patient who has a medical history of and/or current disease including any of the following(s):

a) History of one severe or more than two moderate vertebral fractures per Genant classification as determined by the central reading center

b) Hip fracture

c) History and/or presence of atypical femoral fracture

Reason for exclusion: The exclusion criteria for previous vertebral and hip fractures are based on technical requirements for the reduction of confounding factor impact on efficacy measurements in clinical studies.

Is it considered to be included as missing information?: No

Rationale: Patients with above mentioned exclusion criteria were excluded to prevent interference with efficacy and safety study endpoints.

Patients with history of hyperparathyroidism or hypoparathyroidism, irrespective of current controlled or uncontrolled status; Current hyperthyroidism (unless well controlled on stable antithyroid therapy); Current hypothyroidism (unless well controlled on stable thyroid replacement therapy); History of parathyroid surgery; Current hypocalcemia or hypercalcemia

Reason for exclusion: Parathyroid hormone plays an important role in bone mineral homeostasis and bone density. Both hyperthyroidism and to some extent, hypothyroidism are

associated with altered bone mineral density, which may increase fracture risk. Pre-existing hypocalcaemia must be corrected prior to initiating therapy with Denosumab Ascend.

Is it considered to be included as missing information?: No

Rationale: Denosumab, parathyroid hormone and thyroid hormone all have an effect on bone metabolism and calcium homeostasis. Parathyroid pathology and thyroid abnormalities would potentially have confounded the interpretation of efficacy results in clinical studies. Patients with above mentioned exclusion criteria were excluded to prevent confounding the interpretation of study results of efficacy endpoints.

History of bone disease and metabolic disease (except for osteoporosis) that may interfere with the interpretation of the results including osteomalacia, osteogenesis imperfecta, Paget's disease, rheumatoid arthritis, ankylosing spondylitis, osteopetrosis, fibrous dysplasia, an elevation of ALP at the Investigator's discretion, Cushing's disease, hyperprolactinemia, malabsorption syndrome, advanced scoliosis or extensive lumbar fusion

Reason for exclusion: Patients with other bone diseases (as mentioned in the above exclusion criterion) were excluded from the pivotal study because other bone diseases could confound the efficacy results.

Is it considered to be included as missing information?: No

Rationale: Denosumab is not indicated for use in the patient populations with these types of bone disease.

New York Heart Association (NYHA) Class III or IV chronic heart failure, any unstable cardiovascular disease, pulmonary disease, autoimmune disease or electrocardiogram (ECG) abnormalities which can be judged as clinically significant at the Investigator's discretion

Reason for exclusion: Clinically significant cardiac, pulmonary, or autoimmune disease may complicate the interpretation of safety endpoints. These co-morbidities may also increase risk of hospitalisation and patient dropout.

Is it considered to be included as missing information?: No

Rationale: 'Cardiovascular events' are an important potential risk for denosumab. Patients with above mentioned exclusion criteria were excluded to prevent confounding the interpretation of safety study endpoints.

History and/or current oral or dental conditions including osteomyelitis or osteonecrosis of the jaw (ONJ); active dental or jaw condition which requires oral surgery; planned invasive dental procedure (e.g., tooth extraction, dental implants, oral surgery); unhealed dental oral surgery

Reason for exclusion: While on treatment, invasive dental procedures should be performed only after careful consideration and be avoided in close proximity to denosumab administration.

Is it considered to be included as missing information?: No

Rationale: 'ONJ' is an important identified risk of denosumab (SmPC Section 4.8 [Undesirable effects]). The use of denosumab is contraindicated in patients with unhealed lesions from dental or oral surgery (Section 4.3 [Contraindication]). Routine risk minimisation activities recommending specific clinical measures to address the risk before and during treatment have been adequately described in Denosumab Ascend SmPC (Section 4.4 [Special warnings and precautions for use]).

History of any malignancy within 5 years prior to the first administration of the study drug except adequately treated squamous or basal cell carcinoma of the skin or cervical carcinoma in situ. Any history of bone metastases, implant radiation involving the skeleton, or skeletal malignancies are exclusionary.

Reason for exclusion: Use of any other giant cell tumour of bone-specific treatment would interfere with the ability to assess denosumab's efficacy. Also, the presence of osteosarcoma or other bone tumours could interfere with the ability to assess denosumab's efficacy on giant cell tumour of bone. Additionally, treatment with an immunomodulatory agent may theoretically increase the risk of developing a malignancy. Concurrent or recent malignancy may complicate the interpretation of efficacy and safety endpoints. Moreover, patients with history of past or concurrent malignancy are prone to frequent hospitalisation, hence an increased risk of dropout.

Is it considered to be included as missing information?: No

Rationale: Malignancy is an important potential risk for denosumab (SmPC Section 4.8 [Undesirable effects]), based on theoretical concerns, and have not been substantiated in the extensive clinical study programme or in the postmarketing experience with the reference product Xgeva. Recommendations for monitoring radiological signs of malignancy, new radiolucency or osteolysis are included in SmPC of Denosumab Ascend (Section 4.4 [Special warnings and precautions for use]).

Patient who has a history of and/or concurrent use of medications including any of the following:

Receipt of intravenous bisphosphonates, fluoride, and strontium for osteoporosis within the last 5 years prior to the first administration of the study drug

Receipt of oral bisphosphonates ≥3 years cumulatively prior to Screening or receipt of any dose of oral bisphosphonates within 12 months prior to Screening

Reason for exclusion: Patients who received prior treatment with above mentioned medicinal products were excluded as such treatments could confound the determination of efficacy and safety in clinical studies. Bisphosphonates incorporate into bone and long-term use of bisphosphonates is associated with continued and prolonged activity after the treatment has stopped.

Is it considered to be included as missing information?: Yes (for prior IV bisphosphonate use only)

Rationale: In clinical trials performed with the reference product, denosumab has been administered in combination with standard anti-cancer treatment and in subjects previously

receiving bisphosphonates. There were no clinically-relevant alterations in trough serum concentration and pharmacodynamics of denosumab (creatinine adjusted urinary N-telopeptide, uNTx/Cr) with previous intravenous bisphosphonate exposure. The efficacy and safety of denosumab in patients treated with fluoride, or strontium for osteoporosis have not been established. In clinical trials performed with the reference product, data are available for 795 subjects in advanced cancer settings and an additional 19 subjects that received denosumab from the multiple myeloma pivotal study who had previously received bisphosphonates. A denosumab study was also conducted in cynomolgus monkeys transitioned from bisphosphonate therapy and two clinical studies of bisphosphonate-transition in bone loss settings. Results from these studies did not demonstrate an increased risk of skeletal adverse effects over the period exposed in patients who received denosumab following bisphosphonate use.

Patient who has a history of and/or concurrent use of medications including any of the following:

Use of parathyroid hormone (PTH) or its derivatives, systemic hormone-replacement therapy (estrogen with or without progestogen), selective estrogen-receptor modulator, tibolone, calcitonin, or calcitriol within 12 months prior to the first administration of the study drug

Use of other bone active drugs including heparin, anticonvulsives (except benzodiazepines), systemic ketoconazole, anabolic steroids, testosterone, androgens, adrenocorticotropic hormone, cinacalcet, aluminum, lithium, protease inhibitors, methotrexate, or gonadotropin-releasing hormone agonists within 3 months prior to the first administration of the study drug

Use of oral or parenteral glucocorticosteroids (>5 mg/prednisone daily or equivalent for > 10 days) within 3 months prior to the first administration of the study drug

Reason for exclusion: The medications listed may affect bone turnover, and/or bone density that could interfere with the interpretation of both efficacy and safety outcomes in clinical studies.

Is it considered to be included as missing information?: No

Rationale: Patients with above mentioned received drugs were excluded to prevent interference with efficacy and safety study endpoints.

Patient who has evidence of any other coexisting disease or medical or psychological condition, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational product (IP) or could have interfere with the interpretation of study results, or patient is at high risk for treatment complication in the opinion of the Investigator.

Reason for exclusion: Coexisting conditions may complicate the interpretation of efficacy endpoints and safety results.

Is it considered to be included as missing information?: No

Rationale: The patients were excluded to prevent confounding of efficacy and safety results and to reduce the risk of premature termination of treatment in the study. There are no specific safety concerns associated with this exclusion criterion.

History of any transplant or chronic immunosuppression (including patients on immunosuppressive therapy)

Reason for Exclusion: Patients with a history of organ transplant or those on chronic immunosuppressive therapy are excluded from many clinical trials primarily to mitigate risks to patient safety and to avoid confounding the study's results.

Is it considered to be included as missing information? No.

Rationale: Patients with a history of transplant or immunosuppression face unacceptable safety risks, including life-threatening organ rejection and severe infections if they participate in the trial. The multiple health factors and medications in this group create confounding variables, making it impossible to determine if outcomes are due to the study drug or other causes. Consequently, excluding these patients is essential to protect their safety and ensure the scientific integrity and clarity of the trial's results..

Severe liver dysfunction (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] > 3 times upper limit of normal)

Reason for Exclusion: Patients with severe liver dysfunction, as indicated by significantly elevated liver enzymes (ALT or AST > 3 times the upper limit of normal), are typically excluded from clinical trials to ensure the accurate assessment of the investigational drug's safety and efficacy profile.

Is it considered to be included as missing information? No.

Rationale: The patients were excluded to prevent confounding of efficacy and safety results and to reduce the risk of premature termination of treatment in the study. There are no specific safety concerns associated with this exclusion criterion since Denosumab is composed solely of amino acids and carbohydrates as native immunoglobulin and is unlikely to be eliminated via hepatic metabolic mechanisms. Its metabolism and elimination are expected to follow the immunoglobulin clearance pathways, resulting in degradation to small peptides and individual amino acids.

Major surgery within 8 weeks prior to screening or anticipated major surgery during the study

Reason for Exclusion: To ensure the patient's physiological state is stable and not influenced by the significant stress and inflammatory response of surgery, and to avoid confounding the interpretation of study data.

Is it considered to be included as missing information? No.

Rationale: A major surgery places immense physiological stress on the body. The post-operative period is a vulnerable time characterized by wound healing, systemic inflammation, and a heightened risk of complications like infections. Post-operative patients require medications such as anesthetics, analgesics (painkillers), and antibiotics. A patient recovering

from major surgery may be unable to comply with the demands of the study protocol, such as attending site visits, completing questionnaires, or undergoing study procedures. Furthermore, any post-operative complication would likely necessitate withdrawal from the study, leading to incomplete data and compromising the trial's statistical power.

Clinically significant leukopenia, neutropenia, or anemia as determined by the Investigator or any other clinically significant medical condition or laboratory abnormality that, in the opinion of the Investigator, would pose a risk to patient safety or interfere with adherence to study procedures, study completion, or the interpretation of study results

Reason for Exclusion: Treatment with immunomodulatory agents may increase the risk of infection or worsen an existing infection. Such infections may confound safety evaluation. Moreover, clinically significant leukopenia, neutropenia, or anemia may lead to increased risk of dropout.

Is it considered to be included as missing information? No.

Rationale: Patients with above mentioned conditions were excluded to prevent interference with efficacy and safety study endpoints.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure, due to the limited period of exposure, and the inclusion and exclusion criteria applied to the studies.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Table SIV.1: Exposure of special populations included or not in clinical trial development programmes

Type of special population	**Exposure**
Pregnant women	Not included in the clinical development program
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
Population with relevant different ethnic origin	Not included in the clinical development program
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program
Others: Paediatric patients	Not included in the clinical development program

MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 POST-AUTHORISATION EXPOSURE

Not applicable as the product has not received marketing authorisation yet in any jurisdiction.

SV.1.1 METHOD USED TO CALCULATE EXPOSURE

Not applicable.

SV.1.2 EXPOSURE

Not applicable.

MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

This product has no potential for misuse for illegal purposes.

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 (Xgeva).

SVII.1.2 Risks 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 (Xgeva).

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

Not applicable as this is an initial RMP.

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

Important identified risk: Osteonecrosis of the jaw

Potential mechanisms: ONJ appears to be multifactorial and multiple hypotheses have been postulated and have included factors such as inhibition of bone remodelling, infection and inflammation, inhibition of angiogenesis, soft tissue toxicity, altered immunity and genetic predisposition. As yet, evidence supporting these hypotheses has been variable and little is understood in how these multiple pathways might interact (Fassio et al., 2017; Aghaloo et al., 2015).

Evidence source(s) and strength of evidence:

This risk was identified in randomized, controlled, phase 3 clinical trials conducted with the reference product. This risk was further supported by postmarketing reports with the reference product.

Characterisation of the risk:

In the pivotal study ENZ215-DEN2, there were no Treatment Emergent Adverse Events (TEAEs) reported for osteonecrosis of the jaw in the any group.

Risk factors and risk groups:

Risk factors associated with ONJ include the use of antiresorptives (particularly aminobisphosphonates delivered by intravenous dosing), older age, poor dental hygiene, periodontal disease, invasive dental procedures, trauma from poorly fitting dentures, malignancy, chemotherapy (including antiangiogenesis agents such as bevacizumab), radiation to head and neck, corticosteroids, hypercoagulable state secondary to underlying malignancy, smoking and vascular insufficiency due to thrombosis (Almazrooa et al., 2009; Estilo et al., 2008; Mehrotra et al., 2006; Ruggiero et al., 2006).

Preventability:

A dental examination with appropriate preventive dentistry is recommended prior to treatment with Osenvelt, especially in patients with risk factors. The patients should be encouraged to maintain good oral hygiene, receive routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling, or non-healing of sores or discharge during treatment with denosumab. While on treatment, invasive dental procedures should be performed only after careful consideration and be avoided in close proximity to Osenvelt administration. Patients who are suspected of having, or who develop ONJ while on Osenvelt should receive care by a dentist or an oral surgeon. In patients who develop ONJ during treatment with Osenvelt, a temporary interruption of treatment should be considered until the condition resolves and contributing risk factors are mitigated where possible.

Impact on the risk-benefit balance of the product:

The risk of ONJ events has been considered in the product benefit-risk assessment. In light of the product labelling and a patient reminder card that has been proposed to minimise this risk, the overall benefit-risk balance is considered to be favourable.

Public health impact:

Significant public health impact is not expected based on the relative frequency observed in clinical trials and with the observations that most ONJ events appear to be moderate to severe in severity and resolve without requiring extensive surgical treatment.

Important identified risk: Atypical femoral fracture

Potential mechanisms:

Prolonged suppression of bone turnover may be associated with increased risk of AFF, but the pathogenesis remains unclear and causes of AFF are likely multifactorial. Based on nonclinical studies of bisphosphonates, collagen cross-linking and maturation, accumulation of micro damage and advanced glycation end products, mineralisation, remodelling, vascularity, and angiogenesis lend biologic plausibility to a potential association between these effects and AFF (Ismail et al., 2018; Shane et al., 2010).

Evidence source(s) and strength of evidence:

This risk was identified in randomized, controlled, phase 3 clinical trials conducted with the reference product. This risk was further supported by postmarketing reports with the reference product.

Characterisation of the risk:

In the pivotal study ENZ215-DEN2, there were no Treatment Emergent Adverse Events (TEAEs) reported for osteonecrosis of the jaw in the any group.

Risk factors and risk groups:

Long-term anti-resorptive 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). AFFs have also been reported in patients with certain comorbid conditions (e.g., vitamin D deficiency, rheumatoid arthritis [RA], hypophosphatasia) and with use of bisphosphonates, glucocorticoids, and proton pump inhibitors (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 events has been considered in the product benefit-risk assessment. In light of the product labelling that has been proposed to minimise this risk, the overall benefit-risk balance is considered to be favourable.

Public health impact:

Based on the frequency of AFF, the size of the indicated populations, and usage patterns of denosumab in clinical practice, no significant additional public health impact is expected.

Important identified risk: Hypercalcaemia several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons

Potential mechanisms:

The mechanism(s) of hypercalcaemia several months after the last dose of denosumab in patients with GCTB and in patients with a growing skeleton are not well characterised, but may be a consequence of the following, alone, or in combination:

- Denosumab treatment and resultant RANK/RANKL pathway inhibition in adults with giant-cell containing lesions such as GCTB leads to histopathologic evidence of a dramatic decrease in osteoclast-like giant cells which is complemented by woven bone formation and calcification within the tumours and even at sites of distant metastases (Ghermandi et al., 2016; Yamagishi et al., 2016; Branstetter et al., 2012).
- It is possible this calcium could serve as a depot that is mobilised with reactivation of tumour-associated, RANKL driven giant cell mediated osteolysis following cessation of denosumab.
- Hypercalcaemia may result from rapid resorption of retained primary spongiosa in a skeleton with active endochondral ossification such as in patients with a growing skeleton.

- The rate of endochondral ossification and duration of exposure to denosumab would determine the amount of accumulated primary spongiosa that could influence the magnitude of resorptive response (mechanostat-driven) and release of calcium from the skeleton either near the growth plates (as can be the case with the young adult and adolescent patients) or from the giant cell tumours themselves that have partially ossified in the case of the adult patients with tumour recurrence via an autocrine/paracrine mechanism (Cowan et al., 2011).
- The magnitude of the resorptive response following treatment withdrawal in the patients with GCTB and in those with an immature skeleton could be dictated by the normal high rate of bone turnover within the GCTB lesion or in the growing skeleton of young patients.
- The response of the osteoclast lineage to loss of inhibition of osteoclastogenesis may be intrinsically more robust in young individuals or may be affected by intratumour signalling pathways (e.g., parathyroid hormone-related protein) in GCTB.

Evidence source(s) and strength of evidence:

Clinically significant hypercalcaemia requiring hospitalisation, including hypercalcaemia, complicated by acute renal injury has been reported in denosumab-treated patients with giant cell tumour of bone weeks to months following treatment discontinuation.

In the clinical development programme of the reference product, the frequency of hypercalcaemia in patients with GCTB following discontinuation of denosumab was 0.8 events per 100 subjects, which corresponds to an uncommon frequency (≥0.1% and <1%). All subjects had acute renal injury and all were hospitalised.

In addition, clinically significant cases of post-treatment hypercalcaemia have been identified from literature case reports of denosumab use in paediatric patients for unapproved indications such as fibrous dysplasia, aneurysmal bone cysts, and juvenile Paget's disease. The severity of the events in the postmarketing literature case reports appears qualitatively similar.

Characterisation of the risk:

There are no data for the important identified risk of hypercalcaemia several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons because patients with giant cell tumour of bone or paediatric patients were not included in the study ENZ215-DEN2.

Risk factors and risk groups:

Patients with GCTB and young patients with growing skeletons following discontinuation of denosumab. In general, the most common cause of hypercalcaemia in humans is hyperparathyroidism, particularly among women and individuals aged 65 years or older (Minisola et al., 2015). Hyperthyroidism and rhabdomyolysis associated with renal failure also increase the risk of hypercalcaemia, as does the ingestion of large of amounts of calcium through dairy products or through liberal use of calcium supplements (Machado et al., 2015, Minisola et al., 2015).

Preventability:

No preventive measures are known. After treatment discontinuation, patients should be monitored for signs and symptoms of hypercalcaemia. Periodic serum calcium assessments should be conducted for at-risk patients as clinically indicated. The need for calcium and vitamin D supplementation should be reassessed if denosumab is discontinued. Osenvelt is not recommended in patients with growing skeletons.

Impact on the risk-benefit balance of the product:

The risk of hypercalcaemia events several months after the last dose in patients with GCTB and in patients with growing skeletons has been considered in the product benefit-risk assessment. In light of the product labelling that has been proposed to minimise this risk, the overall benefit-risk balance is considered to be favourable.

Public health impact:

No significant public health impact is expected as hypercalcaemia several months after the last dose in patients with GCTB occurs uncommonly and GCTB is a rare tumour. Off-label use of denosumab in paediatric patients appears to be limited to rare conditions for which there is significant unmet medical need.

Important potential risk: Cardiovascular events

Potential mechanisms:

Elevated levels of OPG have been associated with coronary artery disease in cross-sectional studies, but this association has been contradicted by preclinical and epidemiological studies demonstrating that the lack of OPG or unopposed RANKL is associated with cardiac calcification. Because of these conflicting results and because denosumab inhibits RANKL, a theoretical concern for denosumab to affect progression of atherosclerosis exists.

Evidence source(s) and strength of evidence:

The risk of cardiovascular events is a regulatory concern based on the epidemiological association between OPG levels and cardiovascular disease in humans. Clinical data have not substantiated a cause-and-effect between OPG and atherosclerotic processes nor between denosumab or inhibition of RANKL and undesirable cardiovascular outcomes. In pooled pivotal solid tumour studies with the reference product, subject incidence of cardiovascular adverse events was 29.7% in both treatment groups; the hazard ratio was 0.98 (95% CI: 0.89, 1.08). In a study with denosumab 120 mg Q4W in subjects with castration-resistant prostate cancer (Study 20050147), the subject incidence of cardiovascular adverse events was 33.1% in the denosumab group. In a multiple myeloma study, the subject incidence of adverse events of cardiac disorders was 11.6% and vascular disorder was 20.9% in the denosumab group.

Characterisation of the risk:

In the pivotal study ENZ215-DEN2, overall, there were 20 TEAEs in 14 patients related to cardiovascular events; there were 10 (2.8%) TEAEs reported in 07 patients in the ENZ215

group during the Double-blind Treatment Period and in Prolia® group during the same period there were 10 (2.8%) TEAEs reported in 07 patients.

Frequency with Severity, Seriousness and Outcome:

	ENZ215	Prolia®
Total Number of TEAEs	10	10
Number of Patients with TEAEs	7	7
Proportion of Patients with TEAEs	2.8	2.8
Severity		
Missing	0	0
Mild	6	6
Moderate	4	3
Severe	0	1
Seriousness		
Non-serious	8	8
Serious	2	2
Outcomes		
Missing/Unknown	0	0
Recovered/Resolved	4	2
Recovered/Resolved with Sequelae	0	1
Recovering/Resolving	0	0
Not recovered/Not resolved	6	7
Fatal	0	0

In the pivotal study ENZ215-DEN2, there was one (1.7%) Treatment Emergent Adverse Events (TEAEs) reported in one patient in the Prolia® group during the Open-label Extension Period. No TEAEs were reported in the ENZ215 group during this period.

Frequency with Severity, Seriousness and Outcome:

	ENZ215	Prolia®
Total Number of TEAEs	0	1
Number of Patients with TEAEs	0	1
Proportion of Patients with TEAEs	0	1.7
Severity	--	--
Missing	0	0
Mild	0	1
Moderate	0	0
Severe	0	0
Seriousness	--	--
Non-serious	0	1
Serious	0	0
Outcomes	--	--
Missing/Unknown	0	0
Recovered/Resolved	0	0
Recovered/Resolved with Sequelae	0	0
Recovering/Resolving	0	0
Not recovered/Not resolved	0	1
Fatal	0	0

Risk factors and risk groups:

The denosumab development programme 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., 2004; Hak et al., 2000). Risk factors for atherosclerosis include age, gender, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes, and concomitant medications, including antipsychotic agents and cyclooxygenase-2 (COX-2) inhibitors (Murphy et al., 2007; Smith et al., 2004).

Preventability:

Based on clinical data to date, denosumab has not been categorically associated with an increased incidence or severity of cardiovascular adverse effects; therefore, no preventive measures are defined.

Impact on the risk-benefit balance of the product:

The risk of cardiovascular events has been considered in the product benefit-risk assessment, and the overall benefit-risk balance is favourable.

Public health impact:

Significant public health impact on cardiovascular disease severity or incidence is not expected based on the evidence from denosumab clinical studies in the advanced cancer and postmenopausal osteoporosis/hormone ablation therapy settings.

Important potential risk: Malignancy

Potential mechanisms:

The potential risk of malignancy is based on the theoretical concern that RANKL inhibition may lead to an increased risk for a new primary malignancy (NPM) by impairing immune surveillance mechanisms.

Evidence source(s) and strength of evidence:

In the clinical development programme of the reference product, an imbalance was observed in the NPM events between the zoledronic acid and denosumab treatment groups. The results of a postmarketing retrospective cohort study, showed NPM incidence rates for denosumab were generally lower than those for zoledronic acid in unadjusted analyses, suggesting no obvious excess risk associated with denosumab.

Characterisation of the risk:

In the pivotal study ENZ215-DEN2, overall, there were 15 TEAEs in 12 patients related to malignany events; there were 06 (1.6%) TEAEs reported in 04 patients in the ENZ215 group during the Double-blind Treatment Period and in Prolia® group during the same period there were 09 (3.2%) TEAEs reported in 08 patients.

Frequency with Severity, Seriousness and Outcome:

	ENZ215	Prolia®
Total Number of TEAEs	6	9

Number of Patients with TEAEs	4	8
Proportion of Patients with TEAEs	1.6	3.2
Severity		
Missing	0	0
Mild	4	5
Moderate	2	3
Severe	0	1
Seriousness		
Non-serious	5	5
Serious	1	4
Outcomes		
Missing/Unknown	0	0
Recovered/Resolved	0	4
Recovered/Resolved with Sequelae	0	0
Recovering/Resolving	0	0
Not recovered/Not resolved	6	5
Fatal	0	0

In the pivotal study ENZ215-DEN2, there was 2 (3.3%) Treatment Emergent Adverse Events (TEAEs) reported in 2 patients in the ENZ215 group during the Open-label Extension Period. No TEAEs were reported in the Prolia® group during this period.

Frequency with Severity, Seriousness and Outcome:

	ENZ215	Prolia®
Total Number of TEAEs	2	0
Number of Patients with TEAEs	2	0
Proportion of Patients with TEAEs	3.3	0

Severity	--	--
Missing	0	0
Mild	2	0
Moderate	0	0
Severe	0	0
Seriousness	--	--
Non-serious	2	0
Serious	0	0
Outcomes	--	--
Missing/Unknown	0	0
Recovered/Resolved	0	0
Recovered/Resolved with Sequelae	0	0
Recovering/Resolving	0	0
Not recovered/Not resolved	2	0
Fatal	0	0

Risk factors and risk groups:

General factors for increasing risk of NPM include advancing age, diet, cigarette smoking, excessive ethanol consumption, and numerous environmental toxins. In addition, advanced cancer populations are at increased risk for NPM because of their existing malignancy, possible genetic predisposition, and exposure to chemotherapy and radiation treatment.

Preventability:

There are no known effective preventive measures. Second malignant neoplasms have become increasingly recognised, and current recommendations include vigilance for these cancers in adult cancer survivors.

Impact on the risk-benefit balance of the product:

The risk of malignancy events has been considered in the product benefit-risk assessment. In light of the product labelling that has been proposed to minimise this risk, the overall benefit-risk balance is considered to be favourable.

Public health impact:

Significant public health impact is not expected based on the information from studies in the postmenopausal osteoporosis/ hormone ablation therapy and advanced cancer settings.

Important potential risk: Delay in diagnosis of primary malignancy in giant cell tumour of bone (GCTB)

Potential mechanisms:

At the time of GCTB diagnosis, primary malignancy in giant cell tumour of bone (PMGCTB) may be missed and benign GCTB may be presumed. Based on the mechanism of action and pathology of GCTB, denosumab is only expected to treat benign GCTB. However, there was a theoretical concern that treatment of an undiagnosed PMGCTB with denosumab could delay the diagnosis of PMGCTB.

Evidence source(s) and strength of evidence:

The risk of delay in diagnosis of PMGCTB is a regulatory concern based on the difficulties in diagnosing PMGCTB in a study with the reference product. In clinical studies in GCTB, based on medical review, 11 subjects (2.1%; N=523 had GCTB bone malignancies. Of these, 5 subjects (1.0%) had PMGCTB.

Characterisation of the risk:

There are no data for the important potential risk of delay in diagnosis of primary malignancy in giant cell tumour of bone because patients with giant cell tumour of bone were not included in the study ENZ215-DEN2.

Risk factors and risk groups:

Patients with GCTB are known to be at risk for PMGCTB.

Preventability:

No preventive measures are known.

Impact on the risk-benefit balance of the product:

The risk of delay in diagnosis of PMGCTB events has been considered in the product benefit-risk assessment. In light of the product labelling that has been proposed to minimise this risk, the overall benefit-risk balance is considered to be favourable.

Public health impact:

Given that GCTB is very rare condition, no impact on public health is expected.

Important potential risk: Hypercalcaemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons

Potential mechanisms:

The pathogenesis of hypercalcaemia several months after the last dose in patients other than those with GCTB or growing skeletons may be a consequence of the transient increase in

bone turnover activity. Upon cessation of denosumab, the disinhibition of RANKL allows for terminal differentiation and activation of osteoclasts, which were suppressed during treatment. In patients with underlying causes for calcium dyscrasias (i.e., subclinical hyperparathyroidism), denosumab discontinuation, with its transient increase in bone remodelling and accompanying release of bone mineral, could theoretically be associated with transient hypercalcaemia in susceptible individuals if the normal homeostatic mechanisms regulating serum calcium are not appropriately maintained.

Evidence source(s) and strength of evidence:

Hypercalcaemia after several months of the last dose in patients other than those with GCTB or growing skeletons is a theoretical concern based on the identified risk in other specific populations, GCTB, and paediatric populations. Cases of hypercalcaemia in the off-treatment period have been reported in clinical studies of the reference product, but given the disease state of the subjects, as well as other confounding factors, the occurrence of hypercalcaemia in patients other than those with GCTB or with growing skeletons could not be attributed to discontinuation of denosumab based on available information. As the mechanism for the identified risk in the susceptible populations is not well understood, a theoretical risk remains in other patient groups.

Characterisation of the risk:

There are no data for the important potential risk of hypercalcaemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons were not included in the study ENZ215-DEN2.

Risk factors and risk groups:

Patients other than those with GCTB or growing skeletons following cessation of denosumab.

Preventability:

No preventive measures are known.

Impact on the risk-benefit balance of the product:

The risk of hypercalcaemia events following treatment discontinuation in patients other than those with GCTB or growing skeletons has been incorporated in the product benefit-risk assessment, and the overall benefit-risk balance remains favourable.

Public health impact:

No significant public health impact is expected as the potential events remain infrequent despite extensive market exposure.

MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1: Summary of safety concerns

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

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

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance will be conducted for Denosumab Ascend detailed in corresponding pharmacovigilance procedures that are in place at the MAH as described in Pharmacovigilance System Master File.

Specific adverse reaction follow-up questionnaires:
Targeted follow-up questionnaires will be used for serious adverse events of the risks listed below:

- Osteonecrosis of the jaw
- Atypical femoral fracture

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are intended for Denosumab Ascend.

III.3 Summary Table of Additional Pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable. No post-authorisation efficacy studies are planned by the MAH.

PART V: RISK MINIMISATION MEASURES

V.1 Routine Risk Minimisation Measures

Safety concern	Routine risk minimisation measures
Important Identified risk - Osteonecrosis of the jaw	Routine risk communication: *SmPC sections 4.3, 4.4, 4.8 and 5.1* *PIL sections 2 and 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Recommendations for dental examination prior to/during treatment, maintenance of good oral hygiene during treatment, immediate report of any oral symptoms, and management plan if osteonecrosis of the jaw occurs are included in SmPC section 4.4.*
	Other routine risk minimisation measures beyond the Product Information: Prescription only medicine

Safety concern	Routine risk minimisation measures
Important Identified risk - Atypical femoral fracture	Routine risk communication *SmPC sections 4.4 and 4.8* *PIL sections 2 and 4* Routine risk minimisation 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.*
	Other routine risk minimisation measures beyond the Product Information: Prescription only medicine

Safety concern	Routine risk minimisation measures
Important Identified risk - Hypercalcaemia several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons	Routine risk communication *SmPC sections 4.4 and 4.8* *PIL sections 2 and 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Recommendations for monitoring potential signs and symptoms of hypercalcaemia and evaluating serum calcium periodically after treatment discontinuation are included in SmPC section 4.4 and section 4 of the PL*
	Other routine risk minimisation measures beyond the Product Information: Prescription only medicine

Safety concern	Routine risk minimisation measures
Important Potential risk - Cardiovascular events	Routine risk communication *None* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None proposed.*
	Other routine risk minimisation measures beyond the Product Information: Prescription only medicine

Safety concern	Routine risk minimisation measures
Important Potential risk - Malignancy	Routine risk communication *SmPC sections 4.4, 4.8 and 5.1* *PIL section 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Recommendations for monitoring radiological signs of malignancy, new radiolucency or osteolysis are included in SmPC section 4.4.*
	Other routine risk minimisation measures beyond the Product Information: Prescription only medicine

Safety concern	Routine risk minimisation measures
Important Potential risk - Delay in diagnosis of primary malignancy in giant cell tumour of bone	Routine risk communication *None* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None proposed.*
	Other routine risk minimisation measures beyond the Product Information: Prescription only medicine

Safety concern	Routine risk minimisation measures
Important Potential risk - Hypercalcaemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons	Routine risk communication *None* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None proposed.*
	Other routine risk minimisation measures beyond the Product Information: Prescription only medicine

Safety concern	Routine risk minimisation measures
Missing Information - Patients with previous intravenous treatment with bisphosphonate treatment	Routine risk communication *SmPC sections 4.5 and 5.1* *PL section 2* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None proposed.*
	Other routine risk minimisation measures beyond the Product Information: Prescription only medicine

Safety concern	Routine risk minimisation measures
Missing Information - Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumour of bone	Routine risk communication *None* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None proposed.*
	Other routine risk minimisation measures beyond the Product Information: Prescription only medicine

Safety concern	Routine risk minimisation measures
Missing Information - Off-label use in patients with giant cell tumour of bone that is resectable where resection is unlikely to result in severe morbidity	Routine risk communication *None* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None proposed.*
	Other routine risk minimisation measures beyond the Product Information: Prescription only medicine

V.2. ADDITIONAL RISK MINIMISATION MEASURES

The content and format of the additional risk minimisation measures outlined in this RMP will be agreed and implemented at the national level.

Patient reminder card for Osteonecrosis of the jaw (ONJ)

Objectives:

- To remind the patient to tell his/her doctor of important symptoms that may suggest that he/she may have developed ONJ on the reminder card.

- To provide the patient with a document that he/she can show to any health professional that may not be familiar with the treatment he/she is receiving.
- Patients are to be provided with the patient reminder card for the following risk:
  - Osteonecrosis of the jaw

Rationale for the additional risk minimisation activity:

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 Ascend injections for cancer-related conditions. Also, to ensure that the patient is aware that regular dental examination and good oral hygiene should be maintained during treatment and that he/she should contact the relevant healthcare professional quickly for problems that may arise with the teeth and gums

Target audience and planned distribution path:

Patients who receive Denosumab Ascend must be given a patient reminder card that summarises the safety information about the medicine. The patient reminder card is distributed to healthcare professionals with instruction to provide it to patients.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Evaluation of the effectiveness of the proposed risk minimisation activities will be performed through routine pharmacovigilance activities including signal detection activities. The evaluation of potential new signals is performed mainly using safety data from the review of spontaneous reports, from healthcare professional, consumers, regulatory authority or other organisation, as well as literature reports retrieved from the worldwide literature search. Risk Minimisation Measures are judged effective if no negative trends or worsening outcomes are identified regarding the safety concerns.

V.3 Summary table of risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Osteonecrosis of the jaw	Routine risk minimisation measures: *Wording in the sections 4.3, 4.4, 4.8 and 5.1 of SmPC* *Wording in the sections 2 and 4 of PIL* Other routine risk minimisation measures beyond the Product Information: Prescription only medicine Additional risk minimisation measures: *Patient reminder card.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire Additional pharmacovigilance activities: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Atypical femoral fracture	Routine risk minimisation measures: *Wording in the sections 4.4 and 4.8 of SmPC*	Routine pharmacovigilance activities beyond adverse

	Wording in the sections 2 and 4 of PIL Other routine risk minimisation measures beyond the Product Information: Prescription only medicine Additional risk minimisation measures: *None proposed.*	reactions reporting and signal detection: Targeted follow-up questionnaire Additional pharmacovigilance activities: None.

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Important identified risks		
Hypercalcaemia several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons	Routine risk minimisation measures: *Wording in the sections 4.4 and 4.8 of SmPC* *Wording in the sections 2 and 4 of PIL* Other routine risk minimisation measures beyond the Product Information: Prescription only medicine Additional risk minimisation measures: *None proposed.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None.

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Important Potential risks		
Cardiovascular events	Routine risk minimisation measures: *None* Other routine risk minimisation measures beyond the Product Information: Prescription only medicine Additional risk minimisation measures: *None proposed.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None.

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Important Potential risks		
Malignancy	Routine risk minimisation measures: *Wording in the sections 4.8 and 5.1 of SmPC* *Wording in the section 4 of PIL* Other routine risk minimisation measures beyond the Product Information: Prescription only medicine	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None.

	Additional risk minimisation measures: *None proposed.*	

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Potential risks		
Delay in diagnosis of primary malignancy in giant cell tumour of bone	Routine risk minimisation measures: *None* Other routine risk minimisation measures beyond the Product Information: Prescription only medicine Additional risk minimisation measures: *None proposed.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Potential risks		
Hypercalcaemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons	Routine risk minimisation measures: *None* Other routine risk minimisation measures beyond the Product Information: Prescription only medicine Additional risk minimisation measures: *None proposed.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing information		
Patients with previous intravenous treatment with bisphosphonate treatment	Routine risk minimisation measures: *Wording in the sections 4.5, and 5.1 of SmPC* *Wording in the section 2 of PIL* Other routine risk minimisation measures beyond the Product Information: Prescription only medicine Additional risk minimisation measures: *None proposed.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing information		
Safety with long-term	Routine risk minimisation measures:	Routine pharmacovigilance

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing information		
treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumour of bone	*None* Other routine risk minimisation measures beyond the Product Information: Prescription only medicine Additional risk minimisation measures: *None proposed.*	activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing information		
Off-label use in patients with GCTB that is resectable where resection is unlikely to result in severe morbidity	Routine risk minimisation measures: *None* Other routine risk minimisation measures beyond the Product Information: Prescription only medicine Additional risk minimisation measures: *None proposed.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Denosumab Ascend

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

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

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

I. The medicine and what it is used for

Denosumab Ascend is authorised for the prevention of skeletal related events in adults with advanced malignancies involving bone and treatment of adults and skeletally mature adolescents with giant cell tumour of bone (see SmPC for the full indication). It contains denosumab as the active substance and it is given by subcutaneous route.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Denosumab Ascend, together with measures to minimize such risks, are outlined below.

Measures to minimise the risks identified for Denosumab Ascend:

- Specific information, including 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 authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures will constitute routine risk minimisation measures.

In the case of Denosumab Ascend, these measures are supplemented with additional risk minimization measures mentioned under relevant risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

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

II.A List of important risks and missing information:

Important risks of Denosumab Ascend are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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 Denosumab Ascend. 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);

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

II.B Summary of important risks

Important identified risk: Osteonecrosis of the jaw	
Evidence for linking the risk to the medicine	Osteonecrosis of the jaw (ONJ) is a condition where the jawbone is not covered by the gums and is exposed. It can be caused by two types of medicines: Antiresorptive medicines (including bisphosphonates (BPs) and receptor activator of nuclear factor kappa-B ligand [RANK-L] inhibitors) and antiangiogenic medicines. In the clinical development programme of the reference product, the subject incidence of ONJ was 1.8% in the denosumab group. In a multiple myeloma study, the subject incidence of ONJ was 4.1% in the denosumab group. The incidence of ONJ increased with longer duration of treatment with denosumab. In a post-marketing study with the reference product, the incidence of ONJ per 100 person-years was 3.0 (2.3, 3.7) in patients that started treatment with denosumab, and 4.3 (2.8, 6.3) in patients who switched to denosumab from alternative treatment.
Risk factors and risk groups	Risk factors associated with ONJ include the use of antiresorptives (particularly aminobisphosphonates delivered by intravenous dosing), older age, poor dental hygiene, periodontal disease, invasive dental procedures, trauma from poorly fitting dentures, malignancy, chemotherapy (including antiangiogenesis agents such as bevacizumab), radiation to head and neck, corticosteroids, hypercoagulable state secondary to underlying malignancy, smoking and vascular insufficiency due to thrombosis.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> Wording in the sections 4.3, 4.4, 4.8 and 5.1 of SmPC Wording in the sections 2 and 4 of PIL <u>Other routine risk minimisation measures beyond the Product Information:</u> Prescription only medicine <u>Additional risk minimisation measures:</u> Patient reminder card.

Important identified risk: Atypical femoral fracture	
Evidence for linking the risk to the medicine	In the clinical development programme of the reference product, 0.2% (15 of 8342) of all subjects who received at least one dose of denosumab experienced atypical femoral fracture (AFF). AFF has been reported uncommonly in patients treated with denosumab and the risk increased with longer duration of treatment. Events have occurred during treatment and up to 9 months after treatment was discontinued.
Risk factors and risk groups	Long-term anti-resorptive treatment has been associated with AFF. Corticosteroids have also been reported in the literature to potentially be associated with AFF. AFFs have also been reported in patients with certain comorbid conditions (e.g., vitamin D deficiency, rheumatoid arthritis [RA], hypophosphatasia) and with use of bisphosphonates, glucocorticoids, and proton pump inhibitors.
Risk minimisation measures	Routine risk minimisation measures: Wording in the sections 4.4 and 4.8 of SmPC Wording in the sections 2 and 4 of PIL Other routine risk minimisation measures beyond the Product Information: Prescription only medicine Additional risk minimisation measures: None proposed.

Important identified risk: Hypercalcaemia several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons	
Evidence for linking the risk to the medicine	Clinically significant hypercalcaemia requiring hospitalisation, including hypercalcaemia, complicated by acute renal injury has been reported in denosumab-treated patients with giant cell tumour of bone weeks to months following treatment discontinuation. In the clinical development programme of the reference product, the frequency of hypercalcaemia in patients with GCTB following discontinuation of denosumab

	was 0.8 events per 100 subjects, which corresponds to an uncommon frequency (≥ 0.1% and < 1%). All subjects had acute renal injury and all were hospitalised. In addition, clinically significant cases of post-treatment hypercalcaemia have been identified from literature case reports of denosumab use in paediatric patients for unapproved indications such as fibrous dysplasia, aneurysmal bone cysts, and juvenile Paget's disease. The severity of the events in the postmarketing literature case reports appears qualitatively similar.
Risk factors and risk groups	Patients with GCTB and young patients with growing skeletons following discontinuation of denosumab. In general, the most common cause of hypercalcaemia in humans is hyperparathyroidism, particularly among women and individuals aged 65 years or older. Hyperthyroidism and rhabdomyolysis associated with renal failure also increase the risk of hypercalcaemia, as does the ingestion of large of amounts of calcium through dairy products or through liberal use of calcium supplements.
Risk minimisation measures	Routine risk minimisation measures: Wording in the sections 4.4 and 4.8 of SmPC Wording in the sections 2 and 4 of PIL Other routine risk minimisation measures beyond the Product Information: Prescription only medicine Additional risk minimisation measures: None proposed.

Important potential risk: Cardiovascular events	
Evidence for linking the risk to the medicine	The risk of cardiovascular events is a regulatory concern based on the epidemiological association between osteoprotegerin (OPG) levels and cardiovascular disease in humans. Clinical data have not substantiated a cause and effect between OPG and atherosclerotic processes nor between denosumab or inhibition of RANKL and undesirable cardiovascular outcomes. In pooled pivotal solid tumour studies with the reference product, subject

	incidence of cardiovascular adverse events was 29.7% in both treatment groups; the hazard ratio was 0.98 (95% CI: 0.89, 1.08). In a study with denosumab 120 mg Q4W in subjects with castration-resistant prostate cancer (Study 20050147), the subject incidence of cardiovascular adverse events was 33.1% in the denosumab group. In a multiple myeloma study, the subject incidence of adverse events of cardiac disorders was 11.6% and vascular disorder was 20.9% in the denosumab group.
Risk factors and risk groups	The denosumab development programme 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. Risk factors for atherosclerosis include age, gender, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes, and concomitant medications, including antipsychotic agents and cyclooxygenase-2 inhibitors.
Risk minimisation measures	Routine risk minimisation measures: None Other routine risk minimisation measures beyond the Product Information: Prescription only medicine Additional risk minimisation measures: None proposed.

Important potential risk: Malignancy	
Evidence for linking the risk to the medicine	In the clinical development programme of the reference product, an imbalance was observed in the new primary malignancy (NPM) events between the zoledronic acid and denosumab treatment groups. The results of a postmarketing retrospective cohort study, showed NPM incidence rates for denosumab were generally lower than those for zoledronic acid in unadjusted analyses, suggesting no obvious excess risk associated with denosumab.

Risk factors and risk groups	General factors for increasing risk of NPM include advancing age, diet, cigarette smoking, excessive ethanol consumption, and numerous environmental toxins. In addition, advanced cancer populations are at increased risk for NPM because of their existing malignancy, possible genetic predisposition, and exposure to chemotherapy and radiation treatment.
Risk minimisation measures	Routine risk minimisation measures: Wording in the sections 4.8 and 5.1 of SmPC Wording in the section 4 of PIL Other routine risk minimisation measures beyond the Product Information: Prescription only medicine Additional risk minimisation measures: None proposed.

Important potential risk: Delay in diagnosis of primary malignancy in giant cell tumour of bone	
Evidence for linking the risk to the medicine	The risk of delay in diagnosis of primary malignancy in giant cell tumour of bone (PMGCTB) is a regulatory concern based on the difficulties in diagnosing PMGCTB in a study with the reference product. In clinical studies in GCTB, based on medical review, 11 subjects (2.1%; N = 523) had GCTB bone malignancies. Of these, 5 subjects (1.0%) had PMGCTB.
Risk factors and risk groups	Patients with GCTB are known to be at risk for PMGCTB.
Risk minimisation measures	Routine risk minimisation measures: None Other routine risk minimisation measures beyond the Product Information: Prescription only medicine Additional risk minimisation measures: None proposed.

Important potential risk: Hypercalcaemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons	
Evidence for linking the risk to the medicine	Hypercalcaemia after several months of the last dose in patients other than those with GCTB or growing skeletons is a theoretical concern based on the identified risk in other specific populations, GCTB, and paediatric populations. Cases of hypercalcaemia in the off-treatment period have been reported in clinical studies of the reference product, but given the disease state of the subjects, as well as other confounding factors, the occurrence of hypercalcaemia in patients other than those with GCTB or with growing skeletons could not be attributed to discontinuation of denosumab based on available information. As the mechanism for the identified risk in the susceptible populations is not well understood, a theoretical risk remains in other patient groups.
Risk factors and risk groups	Patients other than those with GCTB or growing skeletons following cessation of denosumab.
Risk minimisation measures	Routine risk minimisation measures: None Other routine risk minimisation measures beyond the Product Information: Prescription only medicine Additional risk minimisation measures: None proposed.

Missing information: Patients with previous intravenous treatment with bisphosphonate treatment	
Risk minimisation measures	Routine risk minimisation measures: Wording in the sections 4.5, and 5.1 of SmPC Wording in the section 2 of PIL Other routine risk minimisation measures beyond the Product Information: Prescription only medicine Additional risk minimisation measures:

	None proposed.

Missing information: Safety with long term treatment and with long term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumour of bone	
Risk minimisation measures	Routine risk minimisation measures: None Other routine risk minimisation measures beyond the Product Information: Prescription only medicine Additional risk minimisation measures: None proposed.

Missing information: Off label use in patients with giant cell tumour of bone that is resectable where resection is unlikely to result in severe morbidity	
Risk minimisation measures	Routine risk minimisation measures: None Other routine risk minimisation measures beyond the Product Information: Prescription only medicine Additional risk minimisation measures: None proposed.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Denosumab Ascend.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Denosumab Ascend.

PART VII: ANNEXES

List of annexes

Annex 1	EudraVigilance Interface
Annex 2	Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme
Annex 3	Protocols for proposed, on-going and completed studies in the pharmacovigilance plan
Annex 4	Specific adverse drug reaction follow-up forms
Annex 5	Protocols for proposed and on-going studies in RMP part IV
Annex 6	Details of proposed additional risk minimisation activities (if applicable)
Annex 7	Other supporting data (including referenced material)
Annex 8	Summary of changes to the risk management plan over time

Annex 1: EudraVigilance interface

Not applicable.

Annex 2: Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Not applicable.

Annex 3: Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Not applicable

Annex 4: Specific adverse drug reaction follow-up forms

Following follow up questionnaires enclosed:

- Questionnaire for osteonecrosis of the jaw
- Questionnaire for potential atypical fracture

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: _____

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

Event Reported Term

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

Denosumab Indication

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

Denosumab Dose

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

Denosumab Exposure

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

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

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

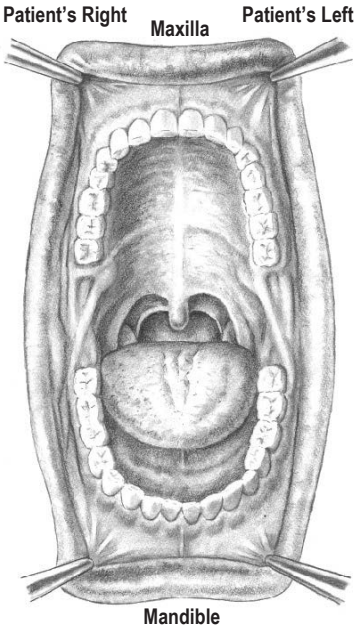
Date exposed bone was first visualized/probed: _____

Exposed bone or probed bone that has persisted for more than eight weeks:
☐No ☐Yes ☐Unknown _____

Prior history of radiation therapy to jaw:
☐No ☐Yes ☐Unknown _____

Prior history of metastatic disease to jaw:
☐No ☐Yes ☐Unknown
Describe: _____
_____

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



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

Oral Findings

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

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

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

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

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

Please describe the clinical signs/symptoms/location:
_____
_____
_____
_____

Ascend
Office Fax:

CONTINUED ON NEXT PAGE

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

Ascend
Office Fax:

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

CONTINUED FROM PREVIOUS PAGE

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

AER #

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

Patient Identifier

Patient Initials

Date of Event Onset

Date of This Report

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

Age at time of event: _____

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)

DENOSUMAB Core Questionnaire

POSTMARKETING REPORTS OF POTENTIAL ATYPICAL FRACTURE

(low energy, subtrochanteric/femoral shaft fractures)

AER #

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

Patient Identifier | Patient Initials | Date of This Report

TREATMENT (Please provide dates and indicate attachments if available)

Methods to reduce and set fracture:

- ☐ Non-surgical reduction _____
- ☐ Casting _____
- ☐ Surgery _____
- ☐ Revision surgery (2nd surgery) _____
- ☐ Other _____
- ☐ Unknown _____

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

General:

- ☐ History or current corticosteroid use
- ☐ Affected hip with prior surgical pinning
- ☐ Affected hip with prior hip replacement

Cancer:

Evidence of any metastases: ☐ Yes ☐ No ☐ Unknown

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

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

Prior osteoporosis therapy:

- ☐ Estrogen
- ☐ Selective estrogen receptor modulator (SERM)
- ☐ Bisphosphonate (please indicate)
  - ☐ Intravenous ☐ Oral
  - If yes, how long has therapy been received? (months, years) _____
- ☐ Parathyroid hormone

Past medical and surgical history: _____

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

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

Ascend
Office Fax:

REPORTER

Name:

Address:

City:

Country:

State/
Province:

Postal Code:

Email:

Phone: (include country code)

Signature _____

Title _____ **Date** _____

Annex 5: Protocols for proposed and on-going studies in RMP part IV

Not applicable.

Annex 6: Details of proposed additional risk minimisation activities (if applicable)

Draft key messages of the additional risk minimisation measures:

Prior to launch of Denosumab Ascend the MAH will agree the content and format of the educational programme, including communication media and distribution modalities with each NCA.

Patient reminder card:

Patient Reminder Cards for osteonecrosis of the jaw (ONJ) will be distributed to healthcare professionals of Denosumab Ascend with instructions to provide it to patients.

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

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

Annex 7: Other supporting data (including referenced material)

Referenced Material:

- Xgeva : Risk-management-plan (Last updated: 04/09/2024): https://www.ema.europa.eu/en/documents/rmp/xgeva-risk-managment-plan_en.pdf

Annex 8: Summary of changes to the risk management plan over time

Version	Approval date Procedure	Change
0.1	-	Not Applicable
0.2	-	• The heading "Patient reminder card for osteonecrosis of the jaw (ONJ)" added before listing the information regarding the patient reminder card in section V.2 Additional Risk Minimisation Measures